Prophylactic platelet transfusions: why less is more

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Prophylactic Platelet Transfusions: Why Less Is More

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KEYWORDS

• Infant • Newborn • Premature • Platelet transfusion • Thrombocytopenia
• Hemorrhage

KEY POINTS

- Three neonatal platelet transfusion trials show no benefit or to varying degrees evidence of harm when applying more liberal platelet transfusion policies.
- We recommend the use of restrictive platelet transfusion thresholds, although recognizing important limitations of these trials.
- Implementation strategies are required to support evidence-based transfusion practices.
- Future research should address the mechanisms of transfusion-related harm and develop more individualized platelet transfusion guidelines.

INTRODUCTION

On March 4, 1908, a term neonate received a blood transfusion for the first time[1]. Since then, the use of blood transfusion components in neonates has steadily increased and has also been adopted into the care of increasingly preterm infants. Platelet transfusions are the second most commonly transfused blood product in neonates, mostly provided with the aim to prevent bleeding, as prophylaxis. In the past, much of the evidence for the safety and efficacy of administering platelets to neonates has been derived from randomized clinical trials (RCTs) in adult patients, often with hematological malignancies, without formal investigation in neonates. This is important, because

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it became increasingly clear that the neonatal hemostatic system differs from that of adults.[2]

When considering the relative benefits and risks of platelets, it should be recognized that all blood components are biological products with risks of transfusion-associated adverse events (eg, transfusion-transmitted infection or transfusion-associated circulatory overload [TACO]) or those related to administration errors. In addition, platelets are recognized to have functions beyond primary hemostasis including inflammatory and immunologic effects, and it has been hypothesized that there is a developmental mismatch between immature neonatal platelets and adult donor platelets, which may have clinical consequences.[3–5]

The first platelet transfusion trial in neonates was published in 1993.[6] This trial aimed to investigate whether early treatment of thrombocytopenia (when platelet counts dropped below 150×10^9/L) would decrease the incidence or extension of intracranial hemorrhage (ICH) compared with initiating treatment at a severe thrombocytopenia threshold of 50×10^9/L. Years after this, in 2019, two other trials have been published comparing restrictive versus liberal transfusion thresholds in preterm neonates.[7,8] These studies recommended the use of lower platelet transfusion thresholds, but the optimal thresholds are still unknown, and there is persistent and widespread variation in clinical practice.

With the publication of the 2-year neurodevelopmental follow-up of the Platelets for Neonatal Transfusion-2/Management of Thrombocytopenia in Special Subgroup (PlaNeT-2/MATISSE) trial and recent publications about variation in neonatal transfusion practice,[9–11] it is time to review the trials and long-term follow-up data, address their limitations, and discuss the challenges and implications for practice and research.

PLATELET TRANSFUSION TRIALS IN PRETERM NEONATES

Three platelet transfusion trials have been conducted to inform the risk–benefit balance for different prophylactic platelet transfusion strategies in preterm neonates. In **Table 1**, we provided an overview of the most relevant trial characteristics and the main results on bleeding, mortality, and neurodevelopmental and respiratory endpoints. We summarized the screening and selection process and the baseline characteristics of these trials in **Fig. 1** and **Table 2**, respectively.

In 1993, Andrew and colleagues performed the first platelet transfusion trial in neonates.[6] The trial compared a liberal (150×10^9/L) versus a restrictive (50×10^9/L) platelet count transfusion threshold to investigate new-onset or extension of ICH (based on the Papile classification[12]). The cohort consisted of 152 preterm neonates with a gestational age (GA) less than 33 weeks and birth weight between 500 and 1500 g. Neonates with initial platelet counts less than 50×10^9/L were excluded. Platelet counts of neonates in the liberal group were maintained greater than 150×10^9/L until day 7 of the study by a maximum of one to three platelet transfusions, whereas infants in the restrictive group did not receive a platelet transfusion unless their platelet count fell to less than 50×10^9/L, or if the infant was bleeding. Cranial ultrasound scans were performed before treatment and repeated on day 7 to 10 of the study. The follow-up was complete for 91% of the neonates. The incidence of new ICH or an existing bleed becoming more extensive was comparable between both groups. However, there was a higher increase in the number of major ICH in the liberal compared with the restrictive group (see **Table 1**). It should be acknowledged that neonatal practice has changed considerably since babies were recruited into this trial, and of course, neonatal intensive care units (NICUs) are now supporting much younger GA infants.

Table 1
Platelet transfusion trials in preterm neonates

	Andrew et al,[6] 1993	Kumar et al,[7] 2019	Curley et al,[8] 2019
Location	4 NICUs in Canada	1 NICU in India	43 NICUs in United Kingdom, Ireland, and the Netherlands
Recruitment period	3-y period (years not specified)	March 2016–April 2017	June 2011–August 2017
Inclusion criteria	• GA <33 weeks • Birth weight 500–1500 g • Platelet count <150 × 10^9/L in the first 72 h of life with initial platelet count ≥50 × 10^9/L	• GA <35 weeks • Hemodynamically significant PDA detected at <14 d of postnatal age • Platelet count <100 × 10^9/L	• GA <34 weeks • Cranial ultrasonography showing no major IVH within 6 h before randomization • Platelet count <50 × 10^9/L
N total included	152	44	660
Intervention	liberal (150 × 10^9/L) vs restrictive (50 × 10^9/L) threshold	liberal (100 × 10^9/L) vs restrictive (20 × 10^9/L) threshold[a]	liberal (50 × 10^9/L) vs restrictive (25 × 10^9/L) threshold
Primary endpoint	New onset or extension of ICH up to day 10 of life	Time between randomization and closure of PDA during study period of 120 h	Composite of death or major bleeding up to day 28 after randomization
Bleeding endpoints	New or more extensive ICH[b]: 28.2% (liberal) vs 25.7% (restrictive), *P* = .73 Proportion of infants who developed a grade III or IV ICH[c] 15.4% (liberal) vs 6.8% (restrictive)	Any grade IVH: 40.9% (liberal) vs 9.1% (restrictive), *P* = .034 Major IVH (grade III/IV): 18.2% (liberal) vs 9.1% (restrictive) *P* = .6	Major bleeding or mortality[b]: 26% (liberal) vs 19% (restrictive) OR 1.57 (95% CI 1.06–2.32), *P* = .02 At least one major bleed through trial day 28: 14% (liberal) vs 11% (restrictive) HR 1.32 (95% CI 1.00–1.74)
Mortality endpoints	11 infants (7.2%) died before reaching day 7–10 of the study (not stratified by intervention arm)	Mortality during study period: 31.8% (liberal) vs 36.4% (restrictive), *P* = .9 Mortality during hospital stay: 36.4% (liberal) vs 40.9% (restrictive), *P* = .9	Death through trial day 28 15% (liberal) vs 10% (restrictive) OR 1.56 (95% CI 0.95–2.55)

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Table 1
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	Andrew et al,[6] 1993	Kumar et al,[7] 2019	Curley et al,[8] 2019
Respiratory endpoints	N/A	N/A	BPD at 36 weeks of PMA: 63% (liberal) vs 54% (restrictive) OR 1.54 (95% CI 1.03–2.30)
Neurodevelopmental outcomes at 2 y of corrected age	N/A	N/A	Death up to 2 y or unfavorable outcome[d]: 50% (liberal) vs 39% (restrictive) OR 1.54 (1.09–2.17), $P = .0167$
Respiratory outcomes at 2 y of corrected age	N/A	N/A	Death or respiratory support required at 2 y: 38% (liberal) vs 28% (restrictive) OR 1.62 (95% CI 1.12–2.34) Respiratory support required at 2 y (excluding deaths): 11% (liberal) vs 4% (restrictive) OR 2.86 (95% CI 1.25–6.51)

Abbreviations: BPD, bronchopulmonary dysplasia; GA, gestational age; HR, hazard ratio; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; N/A, not available; OR, odds ratio; PDA, patent ductus arteriosus; PMA, postmenstrual age.

[a] Depending on clinical criteria: $<20 \times 10^9$/L in non-bleeding neonates, $<50 \times 10^9$/L before a major non-neurosurgical intervention, $<100 \times 10^9$/L before a neurosurgical intervention.

[b] Primary outcome.

[c] Calculations based on Table 2 of Andrew et al: 15.4% ([24/78]–[12/78]) and 6.8% ([14/74]–[9/74]).

[d] Unfavorable outcome defined as cerebral palsy that impaired independent walking; global developmental delay assessed by health care professionals as >9 mo behind expected for age; severe seizure disorder; hearing impairment not correct by hearing aids; or bilateral visual impairment with no useful vision (light perception only).

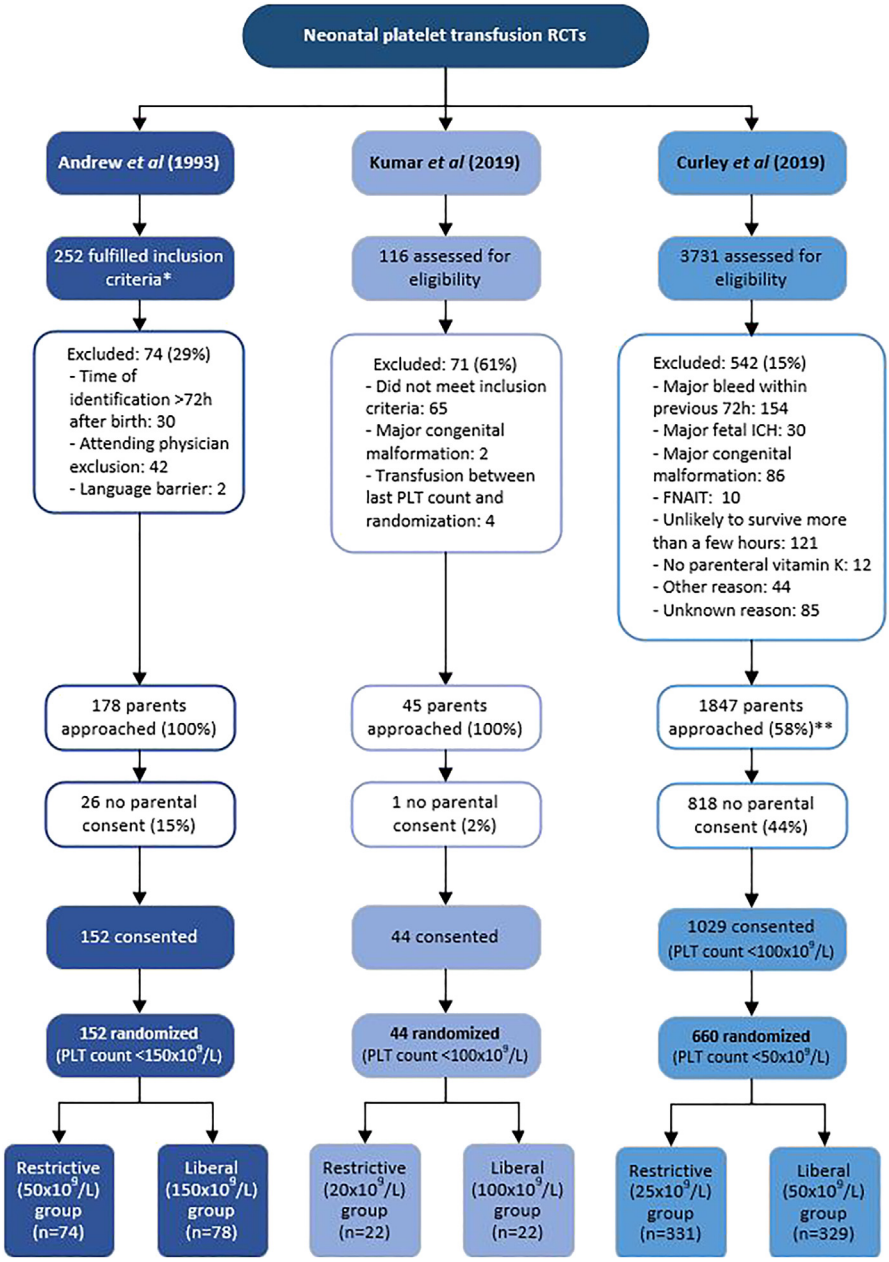

Fig. 1. Screening and selection process of the platelet transfusion trials in neonates. PLT, platelet; ICH, intracranial hemorrhage; FNAIT, fetal and neonatal alloimmune thrombocytopenia. *The total number of neonates checked for eligibility is not reported. **Parents of 1342 neonates were not approached: 559 infants had a PLT count recovery $\geq 100 \times 10^9$/L before consent, 108 parents were too upset to discuss research, 65 stayed too briefly in hospital to permit recruitment, 122 were missed, 348 had another reason, and 140 had an unknown reason.

Table 2
Baseline characteristics of platelet transfusion trials in preterm neonates

	Andrew et al,[6] 1993		Kumar et al,[7] 2019		Curley et al,[8] 2019	
	Restrictive (50×10^9/L) group (n = 74)	Liberal (150×10^9/L) group (n = 78)	Restrictive (20×10^9/L)[a] group (n = 22)	Liberal (100×10^9/L) group (n = 22)	Restrictive (25×10^9/L) group (n = 331)	Liberal (50×10^9/L) group (n = 329)
Gestational age in weeks, mean ± SD or median (IQR)	27.7 ± 2.5	27.4 ± 2.2	30.0 ± 2.0	29.3 ± 2.4	26.7 (24.9–28.7)	26.6 (24.9–28.9)[b]
Birth weight in grams, mean ± SD or median (IQR)	931 ± 266	915 ± 235	1149.1 ± 303.1	1074.7 ± 307.5	743 (605–990)	728 (600–940)[b]
Median weight in grams at randomization (IQR)	N/A	N/A	1060 (913–1275)	984 (808–1171)	892 (670–1190)[c]	860 (668–1170)
Male sex, n(%)	40 (54.0)	49 (62.8)	13 (59.1)	11 (50.0)	191 (57.7)	205 (62.5)[b]
Cesarean delivery, n(%)	N/A	N/A	12 (54.5)	9 (40.9)	201 (61.0)	208 (63.0)[b]
Median postnatal age in days at randomization (IQR)	1.6 (N/A)	1.9 (N/A)	3.0 (2.0–4.2)	3.0 (2.0–4.2)	7.0 (3.7–18.9)	8.4 (4.0–21.0)[b]
Median platelet count (x10^9/L) at enrollment (IQR)	115 (N/A)	111 (N/A)	68 (47–92)	66 (46–91)	38 (28–44)	38 (29–44)[b]
Treatment for NEC at enrollment, n(%)	1 (1.4)	3 (3.8)	N/A	N/A	49 (14.8)	58 (17.7)[b]
Antibiotic treatment for (suspected) sepsis at enrollment, n(%)	N/A	N/A	2 (9.0)	1 (4.5)	206 (62.2)	209 (63.7)[b]
Existing major IVH at enrollment, n(%)	9 (12.2)	12 (15.4)	N/A	N/A	40 (12.1)	39 (11.9)[b]

Abbreviations: Major IVH defined, as intraventricular hemorrhage (IVH) filling at least 50% of a cerebral ventricle; IQR, interquartile range; Major, IVH; N/A, not available; NEC, necrotizing enterocolitis.

[a] Depending on clinical criteria: <20×10^9/L in non-bleeding neonates, <50×10^9/L before a major non-neurosurgical intervention, <100×10^9/L prior to a neurosurgical intervention.

[b] Data were missing for one infant in the liberal threshold group.

[c] Data were missing for one infant in the restrictive threshold group.

A trial by Kumar and colleagues compared a liberal platelet count threshold of 100×10^9/L to a restrictive threshold in which platelet concentrates were transfused per standard criteria: (1) platelet count less than 20×10^9/L, (2) clinical bleed (ie, any visible fresh oral, nasal, endotracheal, gastrointestinal, or skin bleed), (3) platelet count less than 50×10^9/L before a major non-neurosurgical intervention, or (4) less than 100×10^9/L before a neurosurgical intervention.[7] The primary outcome was time to patent ductus arteriosus (PDA) closure and secondary outcomes included new-onset intraventricular hemorrhage (IVH) of any grade and major (grade III/IV) IVH during the study period. The study population consisted of 44 preterm neonates with a GA less than 35 weeks and a hemodynamically significant PDA detected in the first 2 weeks of life. In the liberal group, two platelet transfusions were administered when the platelet count dropped below 50×10^9/L and one platelet concentrate when the platelet count ranged between 50 and 100×10^9/L. The follow-up time was fixed at 5 days for all study participants. Severe IVH was reported to occur in 18% versus 9% of infants in the liberal versus restrictive group, respectively. The incidence of any IVH grade was significantly higher in the liberal group compared with the restrictive group (see **Table 1**). As for the study by Andrew and colleagues, these differences in outcomes of bleeding should be interpreted with caution given the sample size of the trial.

Finally, the PlaNeT-2/MATISSE trial (2019) compared a liberal (50×10^9/L) versus a restrictive (25×10^9/L) platelet count threshold in 660 infants with a GA less than 34 weeks.[8] The primary outcome was a composite of death or major bleeding up to and including day 28. The follow-up was complete for 99% of the neonates. The study showed increased rates of mortality and major bleeding in the liberal versus the restrictive arm. A secondary analysis indicated that the benefit of a restrictive threshold was evident in all neonates, irrespective of their predicted baseline risk of major bleeding and/or mortality.[13] Furthermore, in the liberal group, a higher incidence of the secondary outcome bronchopulmonary dysplasia (BPD) was observed (see **Table 1**). A post hoc analysis of the composite outcome of death or BPD (to allow for deaths before a possible diagnosis of BPD) yielded a similar odds ratio. There was no difference in the secondary outcomes necrotizing enterocolitis (NEC), sepsis, and retinopathy of prematurity.

Parent and public input into neonatal trials have consistently emphasized the importance of longer term neurodevelopmental follow-up. A further publication from the PlaNeT-2/MATISSE research team reported on 2-year follow-up outcomes. In this study, data were obtained for the majority of PlaNeT-2/MATISSE participants (92%) to assess their neurodevelopmental outcomes at a corrected age of 2 years, using a composite of death or unfavorable outcome (ie, neurodevelopmental impairment [NDI] defined as >9 months behind expected for age, cerebral palsy, seizure disorder, profound hearing or vision loss) as a prespecified outcome.[9] Three clinicians, who were blinded for the treatment arm, independently evaluated all available information and reported the outcome on a standardized 2-year outcome form. Using a mixed logistic regression model, the study found that the higher platelet transfusion threshold of 50×10^9/L increased the rate of death or severe NDI at a corrected age of 2 years. However, as only 41% of the children received a formal neurodevelopmental assessment, subtle outcome differences could not be detected. In addition, given the initial finding of a higher incidence of BPD in the liberal threshold group, a post hoc analysis was performed to evaluate the proportion of participants who had died or were dependent on oxygen or respiratory support at 2 years of corrected age, showing a higher need for respiratory support at 2 years among children randomized to the 50×10^9/L threshold group (see **Table 1**).

CHALLENGES IN PLATELET TRANSFUSION TRIALS

The use of randomized controlled trials has been a cornerstone in the development and evaluation of new or existing therapies for preterm infants. However, despite the fact that the platelet trials were designed to minimize bias and test different treatment decisions, they can come with challenges and limitations, which should be considered in the context of implementation of results. In **Table 3**, we discuss several epidemiologic challenges in neonatal transfusion RCTs and consider some of these points from the perspective of the platelet transfusion trials.

One of the main challenges is variation in treatment intervention (including standard of care) between trials, and sometimes also within trials, for instance in multicenter settings. Treatment variation in platelet transfusion trials can occur at several levels. For example, there can be differences in administration (eg, dose and rate) and donor/donation characteristics, such as product specifications (eg, irradiation, pathogen inactivation technologies, storage duration, and differences in the degree of ABO blood group (in)compatibility). As a result of this variation, different trials, and sometimes even different centers within the same trial, are in fact testing different treatments. In general, data on donor and product characteristics are often not readily available to neonatologists. To facilitate assessment of trial generalizability, the intervention under evaluation should be clearly defined and consistent as far as possible within and across trials, including data on component specifications, transfusion volume, and duration.

A further challenge is variation in outcome definitions, including use of composite outcomes, nonformal assessment of long-term outcomes, and definitions of adverse events. Composite outcomes are commonly used in neonatal trials, but there is extensive literature describing the pros and cons of such outcomes.[14,15] Guidelines for the use of composite outcomes suggest that each component should be equally severe and aligned in the same direction of effect, because if the components of the primary outcome change in opposite directions then no effect might be observed, despite a clinically important difference between treatments. An example of this related to platelet transfusion trials is the use of the composite death or an unfavorable outcome at 2 years of corrected age in the PlaNeT-2/MATISSE follow-up, in which NDI may not be considered equally severe as death.[9] In addition, the study was not powered for the long-term follow-up outcome and several assessment tools were used to assess NDI, which also included non-validated tools such as whether the treating physician deemed a child to be impaired, which hampered evaluation of more subtle neurodevelopmental outcome differences. This pragmatic approach to use whatever data are available is understandable, often given the financial and logistical challenges of conducting long-term follow-up studies, but should be recognized, and discussed when developing these studies. Last, in neonatal transfusion trials, adverse effects are often not well-defined and mostly reported at the discretion of neonatologists. We need to improve more neonatal specific definitions for transfusion-associated adverse events, such as transfusion-related acute lung injury, transfusion-related acute lung injury (TACO), and transfusion-associated dyspnea (TAD), and report these in future trials.

Third, pre-randomization transfusions, protocol violations, and lack of blinding are study conduct-related issues that often occur. Pre-randomization transfusions are common in neonatal transfusion trials as a result of a delay caused by the informed consent procedure or babies not being identified on time as eligible for the trial, and possibly also some unease in the mind of attending neonatologists about potential delays to platelet transfusion, particularly in very preterm neonates just after birth. In the PlaNeT-2/MATISSE trial, 39% of the infants received a platelet transfusion before

Table 3
Epidemiologic challenges in neonatal transfusion randomized clinical trials

Issues in/between trial(s)	Examples	Potential Solutions for Future Studies
Between trial and within trial variation in interventions	Differences in: • Donor characteristics • Transfusion product specifications • Transfusion dose and rate • Threshold definitions	• Describe the intervention in a clear and consistent way, including data on component specifications, transfusion volume, and duration
Between trial and within trial variations in outcome definitions	• Incorrect use of composite outcomes • Non-formal assessment of long-term outcomes • Lack of definitions for transfusion-associated adverse events	• Use standardized and objective outcome measures • Reconsider the use of composite outcomes or improve their composition • Perform separate power calculations for long-term outcomes • Improve definitions for neonatal transfusion-associated adverse events and report these in future trials
Study conduct issues	• Pre-randomization transfusions • Protocol violations • Lack of blinding • Inappropriate exclusions	• Facilitate randomization at an early postnatal age by improving consenting procedures • Perform a sensitivity analysis in case of considerable pre-randomization transfusions • Improve protocol adherence in future trials • Record other treatments that might be adjusted based on the assigned transfusion thresholds to evaluate the presence of post-randomization bias
Generalizability/external validity	• Important patient (sub)groups not included in the trials • Relatively high number of parental consent refusals for their child's participation in RCTs	• Choose a study population that is representative of the target population, including analyses to assess heterogeneity of treatment effect • Collaborate with parent representatives of preterm or ill-born neonates • Repeat trials in other settings, including important subgroups (eg, surgical/ECMO patients) that have not yet been evaluated in other trials

Abbreviations: RCTs, randomized controlled trials; ECMO, extracorporeal membrane oxygenation.

randomization (121 in the restrictive group and 126 in the liberal group).[8] These pre-randomization transfusions might affect the trial generalizability and may dilute the treatment effect, as it is possible that these transfusions were given during the highest risk period for ICH. Some of these infants may never have developed platelet counts less than 50×10^9/L after the initial transfusion and were therefore excluded from the trial. Facilitating randomization at an early postnatal age by improving consenting and screening procedures should therefore be a priority in future trials. Additional analyses of the trial data could be performed to investigate the extent to which those transfusions might have impacted the observed treatment effect.

Protocol violations with disbalance between the arms increase the risk of bias toward the null and platelet count separation between trial arms does not guarantee sufficient contrast between the study arms, as in all trials platelet count measurements were done at the discretion of the treating neonatologist. These implications for the PlaNeT-2/MATISSE trial might be limited, as a difference between the arms was still observed despite protocol violations.[8]

The lack of blinding may allow clinicians to adjust the management of neonates consciously or unconsciously depending on the trial arm in which the neonate was randomized, potentially leading to post-randomization bias. However, blinded studies in transfusion are practically very difficult to execute. Future studies should focus on the development of standardized and objective outcome measures and record other treatments that might be adjusted based on the assigned transfusion thresholds to evaluate the presence of post-randomization bias.

Finally, the external validity of neonatal platelet transfusion trials is limited to neonates with comparable characteristics to the study populations. In the PlaNeT-2/MATISSE trial, neonates with early-onset thrombocytopenia (ie, in the first 72 hour after birth) were recruited but perhaps underrepresented. Further important patient (sub)groups that have not been assessed in the trials are neonates with a GA at birth $\geq$35 weeks, neonates with major congenital malformations, those who undergo invasive procedures or surgery, extracorporeal membrane oxygenation (ECMO) patients, neonates with a family history of or confirmed fetal neonatal alloimmunre thrombocytopenia (FNAIT), and actively bleeding neonates. Furthermore, there were a total of 381 neonates in the trials whose parents/guardians were not approached for study participation because they were missed or for unknown reasons, and of the 2070 parents/guardians who were approached, 41% did not provide consent (see **Fig. 1**). Efforts to improve screening for eligibility and optimization of consent procedures are necessary to exclude infants for no other reasons than the prespecified exclusion criteria and to obtain consent as early as possible. Collaboration with parent representatives of preterm or ill-born neonates could help identify barriers for study participation, which could then be addressed to minimize selection bias due to consent refusal.

In summary, future studies might consider these trial design points to help develop more robust studies, alongside general recommendations for the reporting of randomized trials. Other areas to consider, beyond the scope of this review, include analysis plans. Additional subgroup analyses could be performed to assess heterogeneity of treatment effect, such as has been performed for the PlaNeT-2/MATISSE study.[13]

WHAT IS THE EVIDENCE ON UPTAKE OF RESEARCH FINDINGS INTO NEONATAL PRACTICE?

To evaluate the extent to which the results of the platelet transfusion trials reflect and/or have changed platelet transfusion practices in neonatal care, we now summarize

the results of two recently published studies about neonatal platelet transfusion practices in the United States and Europe, respectively.

Patel and colleagues described in a retrospective cohort study the incidence of blood product transfusions in neonates, including platelet transfusions, using data from seven North American tertiary and quaternary NICUs between 2013 and 2016.[10] All birth admissions during the study period of the participating sites were included, resulting in a total cohort of 60.243 infants. Ninety percent of this cohort consisted of term infants (≥37 weeks' gestation), with 329 neonates with a GA less than 27 weeks. The incidence of platelet transfusions was 0.7% (95% CI 0.6%–0.7%) among the full cohort and 35% (95% CI 29%–39%) among preterm infants less than 27 weeks' gestation. The median pre-transfusion platelet count was 71 $\times$ 10^9/L (10th–90th percentile 26–135 $\times$ 10^9/L) for the entire cohort, 85 $\times$ 10^9/L (17–185) for term infants, and 70 $\times$ 10^9/L (33–100) for infants with a GA less than 27 weeks, though this included presurgery thresholds. The highest median pre-transfusion platelet counts (>100 $\times$ 10^9/L) were observed among neonates receiving ECMO for congenital diaphragmatic hernia and/or persisting pulmonary hypertension of the newborn. No distinction could be made between prophylactic transfusions and those administered in response to clinically significant bleeding. This study demonstrated wide variability in neonatal platelet transfusion practices in the United States, with a large proportion of transfusions administered at thresholds higher than currently supported by the best available evidence. Importantly, the study assessed clinical data from before the publication of the PlaNeT-2/MATISSE trial. Several subsequent implementation studies in NICUs in the United States and Canada have been published,[16–18] suggesting that the clinical thresholds may have been lowered since then, though epidemiologic data are lacking.

Scrivens and colleagues also reported substantial ongoing variation in platelet transfusion practices across European centers based on an online survey performed among 597 NICUs in 18 European countries with care for infants less than 32 weeks' gestation.[11] This study was coordinated by the Neonatal Transfusion Network, a recently established international, interdisciplinary research network dedicated to neonatal transfusion research (see https://neonataltransfusionnetwork.com/). The survey included NICUs in the period from October to December 2020, which was 2 years after the publication of the PlaNeT-2/MATISSE trial. In this Survey on Transfusion practices among European Preterm infants admitted to Neonatal Intensive Care Units (STEP), 47% to 57% of the NICUs indicated using platelet transfusion thresholds above 25 $\times$ 10^9/L in non-bleeding neonates. For infants who received ibuprofen for PDA treatment, thresholds ≥25 $\times$ 10^9/L were used in 84% of the NICUs. Thresholds ≤20 $\times$ 10^9/L were used in 27% and 34% of the NICUs for infants with a GA less than 28 weeks and 28 to 32 weeks without bleeding, respectively. In addition to thresholds, there was widespread variation in transfusion volume and duration. National guidelines have been changed to adopt the restrictive platelet count thresholds of 25 $\times$ 10^9/L in at least the United Kingdom and the Netherlands,[19] but this survey showed that on a European scale transfusion thresholds still tend to be more liberal compared with the recommended restrictive threshold based on the PlaNeT-2/MATISSE results,[8] highlighting that this is an important area for further research. A prospective, international, multicenter observational point prevalence study is ongoing and includes data from more than 75 NICUs from 22 European countries, to gain more insight into current neonatal transfusion practices.[20]

In **Fig. 2**, we created a boxplot based on the data of both studies to show the variation in platelet count transfusion thresholds stratified by GA in the US-based and European NICUs. As the two studies presented their data in different ways, we could not

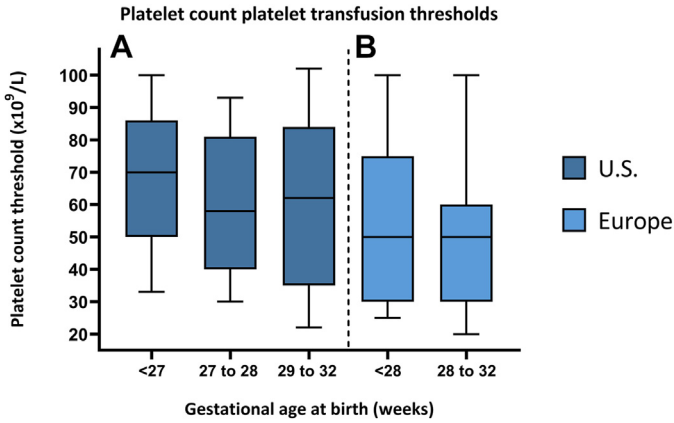

Fig. 2. Boxplot showing the variation in platelet count transfusion thresholds by gestational age in (*A*) US-based NICUs and (*B*) European NICUs. The boxplot's extreme whiskers represent the 10th and 90th percentiles. (*Data from* Patel and colleagues *J. Pediatr.* 2021 and Scrivens and colleagues *Arch Dis Child Fetal Neonatal Ed.* 2023.[10,11])

take into account the variation in transfusion thresholds for different clinical scenarios of thrombocytopenia (eg, surgery, lumbar puncture, ibuprofen) and for transfusions given either prophylactically or in response to bleeding. Although the figure might appear to suggest that higher thresholds are used in the United States compared with Europe, the US data were collected before the publication of the PlaNeT-2/MATISSE trial. The main message of the figure is that it highlights considerable variation in platelet transfusion practice and the need to better understand implementation of neonatal platelet transfusion research findings into clinical practice.[21]

DISCUSSION

In this review, we have summarized the three neonatal platelet transfusion trials, which included a total of 856 neonates. The studies showed no benefit with more liberal platelet transfusion thresholds, and—all to varying degrees—demonstrated some evidence of harm including an increased risk of major bleeding or death associated with the use of more liberal platelet transfusion thresholds. On the other hand, we have identified and discussed potentially important shortcomings and challenges for neonatal platelet transfusion trials.

Recommendations

Despite the limitations of the trials, given the severity of the reported transfusion-related harm and the lack of evidence of benefit for the liberal transfusion thresholds—including 2-year neurodevelopmental outcomes—our overall view is that the trials support the use of restrictive platelet transfusion thresholds. **Box 1** provides a summary of our suggested restrictive policies for platelet transfusions based on the thresholds as tested in the randomized trials. **Box 2** provides a response to common concerns with regard to the recent trials and implementation into clinical practice. Future full systematic reviews, additional analyses and follow-up studies of existing trials, new randomized trials, and complementary observational and translational studies are required to come to more robust recommendations.

In addition, we recommend informing parents about the complexity and uncertainties of transfusion decisions and involving them in the decision-making process.

Box 1
Recommended platelet transfusion thresholds

Patient group	Platelet count threshold
• Non-bleeding preterm neonates (gestational age <37 weeks) not scheduled to undergo an invasive procedure	• 25×10^9/L
• Neonates scheduled to undergo an invasive procedure, who are actively bleeding, or who have experienced major bleeding within the last 72 h	• No recommendation, as these groups were included in trials, but additional transfusions were allowed at the discretion of the treating neonatologist. Current consensus-based guidelines suggest thresholds varying between 50 and 100 $\times 10^9$/L
• Neonates with a major congenital malformation	• No recommendation, as these neonates were excluded from all trials

Of note:
- Any threshold *above the highest recommended* is not evidence-based.
- Any threshold *below the lowest recommended* has not yet been tested (clinical equipoise).

The risk of drafting clinical guidelines with scarce evidence is that this uncertainty is not conveyed to health care professionals, and as a result, is not fully explained to parents. Parents have a right to be made aware of clinical uncertainty and should be informed about the potential benefits and risks of transfusions. In case of clinical equipoise or lack of evidence, their opinion on whether or not their child should receive a blood transfusion becomes even more pivotal.

Future Research Directions

Perhaps one of the bigger challenges in neonatal transfusion medicine is that the platelet transfusion trials were designed as parallel arm studies, comparing only two threshold interventions. Therefore, clinicians are still left without an answer as to what is the optimal threshold for prophylactic platelet transfusions (eg, possibly a threshold of 10×10^9/L or lower). Future clinical transfusion trials might benefit from more innovative designs, such as data-driven embedded trials, adaptive trials, and platform trials. Such studies could also explore the safety of much lower thresholds, for example, platelet counts less than 10×10^9/L which are less commonly seen in practice. In addition to clinical trials, we need a strong emphasis on observational studies and large vein-to-vein data sets to explore associations between donor and product characteristics and clinical outcomes and to benchmark and monitor current practice.

Furthermore, two neonates with similar platelet counts but different clinical conditions may have distinct risks of bleeding and may benefit differently from platelet transfusions. Platelet count-based transfusion thresholds do not accurately identify neonates whose bleeding or death could be prevented by a platelet transfusion from those in which a prophylactic transfusion likely has no effect or might even lead to transfusion-associated adverse events. Incorporating a more personalized approach, for example, by using risk-based thresholds with the use of a validated dynamic prediction model for major bleeding that includes multiple clinical variables in addition to platelet count may perform better and thereby improve patient outcomes.[22] Alternatively, a whole blood test of primary hemostasis, such as the Platelet Function Analyzer Closure Time in response to Collagen and adenosine diphosphate

Box 2
Common concerns regarding platelet transfusion trials and implementation into clinical practice

- **Concern 1: Are the results of the trials valid?**
  We have reviewed the three neonatal platelet transfusion trials and conclude that there are several common limitations among all trials. However, we do consider these trials to be the best evidence currently available to guide clinical transfusion decisions. Future new trials and systematic reviews can be consulted to hopefully verify our findings.
- **Concern 2: I am not certain the results of the trial are generalizable to my center/country.**
  The effects of transfusions will depend on different patient, donor, NICU, product, and administration characteristics. Some of these variables can be compared between the trial population and individual centers or countries, such as neonatal baseline characteristics. Some of the product characteristics are also made explicit in trial publications and could be verified for centers/countries. Unfortunately, for most other variables, it is unknown how and to what extent these differ between the trial populations and individual centers or countries. This makes it difficult to assess whether the trial results may or may not apply, and underlines the need for more studies describing these variables in both the study populations and general neonatal populations. In the meantime, you will have to navigate this uncertainty by estimating to what extent these variables may differ between your center and the trial populations, and to what extent this may affect the outcome of the transfusion strategy. In the absence of the evidence needed to make this assessment, unless there are very strong arguments against this, following the trial recommendations may be the most appropriate strategy.
- **Concern 3: I am not certain the results of the trial apply to a particular subgroup of neonates.**
  Whether the trial results apply to specific subgroups is always a difficult question to answer, because by definition we do not know the answer, as trials are not usually powered for subgroup analyses. As an example, in the PlaNeT-2/MATISSE trial, one of the issues raised in recent opinion papers was the relative lack of early-onset thrombocytopenia in the trial population, as 37% of neonates were randomized before day 5 of life. Some institutions and individual researchers have therefore made an exception in the implementation of the trial results, allowing for higher transfusion thresholds in the first few days of life. This concern is understandable and underlines the need for further studies; however, in our opinion, the translation of subgroup concerns into clinical practice guidelines requires careful assessment of several questions. We have considered these questions for the specific example of early-onset thrombocytopenia in the PlaNeT-2/MATISSE trial.
  1. To what extent is the subgroup represented in the trial? The subgroup is underrepresented: 37% were randomized before the 5th day of life, this should have been around 55% based on Dutch and UK observational studies (Fustolo-Gunnink et al Haematologica. 2019, Figure S3, and Stanworth et al Pediatrics. 2009): median postnatal age of 4 days at first platelet count $<60 \times 10^9$/L, that is, at least 50% of severe thrombocytopenia within the first 4 days of life.[22,23]
  2. Are there signals in the trial that hint at a different effect in the subgroup? No, both the conventional subgroup analysis in the primary paper and a more advanced analysis published separately do not suggest a differential transfusion effect in the first few days of life.[13]
  3. Are there signals in other studies or plausible biological pathways that would justify different treatment in the subgroup? No, to our knowledge, there are no studies that show a differential effect of transfusions depending on postnatal age. The hemostatic system will be more immature in the early days of life, potentially exaggerating the developmental mismatch, but the implications of this mismatch are unknown.[5] The incidence of major bleeding is higher in the first days of life, but this does not imply that transfusions will be (more) effective in preventing these bleeds.
  4. What are the risks of transfusing versus not transfusing in this subgroup?
     - Risk of not transfusing: it is possible that platelet transfusions sometimes, in some neonates, prevent major bleeding. The problem is that we cannot identify these children with our current evidence base.

- Risk of transfusing: 7% overall absolute increase in risk of major bleeding and/or mortality. Within the subgroup of neonates with postnatal age <72 hours at randomization, the risk difference is 14%, though this analysis is underpowered, as mentioned previously.

Our view is that in the specific case of early-onset thrombocytopenia in the PlaNeT-2/MATISSE trial, the weight of the trial results outweighs the risks of a potential differential effect of treatment in this subgroup. We encourage clinicians to address concerns about other subgroups in a similarly structured way.

- **Concern 4: What should be the lowest thresholds for platelet transfusions?**
  The STEP survey indicated that 27% to 34% of the NICUs use platelet thresholds lower than those tested in PlaNeT-2/MATISSE. These NICUs are now faced with the question of whether they should increase their transfusion thresholds. We argue that from a purely scientific point of view, because the lower thresholds have not yet been tested, there is clinical equipoise and therefore clinicians can choose whether or not to transfuse more restrictively. The question is not whether severe thrombocytopenia is harmful to a preterm infant, the question is whether platelet transfusions can mitigate this harm, and whether transfusion-related adverse events outweighs any beneficial effects. As a historical example, in the PlaNeT-1 study, an observational study describing platelet transfusion practices in the United Kingdom, 42% of transfusions were administered at a minimum platelet count of $<25 \times 10^9$/L, which was lower than the recommended thresholds at the time.[23] If this had not been the case, recruitment for the PlaNeT-2/MATISSE trial might have been extremely difficult. In this case, variation in clinical practice was beneficial to the design and conduct of new trials. On the other hand, from an educational/implementation perspective, it may be preferable to define a temporary lower transfusion threshold while awaiting new randomized trials. We suggest that this threshold should be based not only on the trials but also on current clinical practice and could therefore be lower than the lowest ranges tested in the trials.

(ADP), is a promising approach to better predict which babies are more likely to bleed, although the relatively high blood volumes (800 μL) required for this currently hamper its widespread use in the neonatal population.[23] New platelet parameters (eg, immature platelet fraction) are being investigated as markers of bleeding risk in thrombocytopenic preterm neonates, which can be measured simultaneously with platelet count without the need for additional blood.[24] It is essential to conduct quantitative and qualitative studies to investigate differences in clinical context that may explain or justify the use of different transfusion strategies and to understand the barriers and facilitators to translating research findings into clinical practice. Consequently, targeted, tailored implementation studies could help reduce the current evidence-to-practice gap and may be used for the development of improved and individualized guidelines on platelet transfusion in neonates.

Last, the reasons for the observed higher incidence of major bleeding or mortality in the liberal arm of the PlaNeT-2/MATISSE trial are still unknown. Several potential mechanisms of harm have been proposed. First, preterm infants generally receive much higher transfusion volumes compared with adults, circa 15 mL/kg compared with 5 mL/kg, respectively.[11] The rapid volume expansion after administration of a platelet transfusion may induce hemodynamic shifts that could contribute to an increased risk of hemorrhage by disturbing the blood flow in the brain at the location of the germinal matrix. Second, there likely is a developmental mismatch, as there are considerable differences between adult and premature neonatal platelets, including adult platelets being functionally hyperreactive compared with neonatal platelets, but we do not yet fully understand the implications of this mismatch.[5,25,26] Finally, our understanding of the functions of platelets has improved considerably over the last few decades and has revealed a complex interplay between the cellular

and noncellular components of the blood and the immunologic and inflammatory pathways.[2,4] Therefore, it is plausible that transfusion-associated adverse events are (at least in part) related to the immunologic and/or inflammatory properties of platelets.

Because it is very difficult to predict what will happen to adult platelets once they are introduced into a premature neonatal circulatory system, we need high-quality basic research studies to better understand the pathophysiology of neonatal thrombocytopenia and the effects of platelet transfusions. More fundamental and translational research is essential to elucidate the underlying mechanisms of transfusion-related harm to help physicians more accurately determine the risks/benefits of platelet transfusions in thrombocytopenic preterm neonates.

SUMMARY

In short, given the current evidence base, we recommend the use of restrictive platelet transfusion thresholds while awaiting the results of new/ongoing studies and large-scale epidemiologic studies. Future trialists will have an opportunity to address the identified challenges and additionally improve the efficiency and design of these trials using electronic patient data and advanced trial designs. There clearly is a need for new biomarkers and models to better predict bleeding risk for more tailored platelet transfusion decisions, implementation strategies to support evidence-based transfusion practices, and fundamental research to better understand the mechanisms of transfusion-related harm.

Best Practices Box

What is the current practice for neonatal thrombocytopenia?

There is a widespread variation in platelet transfusion practices for the management of neonatal thrombocytopenia. Three platelet transfusion trials in preterm neonates showed no benefit with higher transfusion thresholds. The most recent trial (PlaNeT-2/MATISSE) demonstrated an increased risk of major bleeding or mortality when applying more liberal transfusion policies, with a higher rate of death or significant neurodevelopment impairment at a corrected age of 2 years.

What changes in current practice are likely to improve outcomes?

Despite the potentially important shortcomings of the neonatal platelet transfusion trials and the challenges of translating these research findings into neonatal practice, we believe that they support the paradigm shift from "*better safe than sorry*" to "'*less is more.*" While awaiting the results of new/ongoing studies to address the identified challenges in neonatal transfusion trials (**Table 3** and **Box 2**) and to better understand the mechanisms of transfusion-related harm, following the recommendations of the PlaNeT-2/MATISSE trial is likely the most appropriate strategy to improve neonatal outcomes.

Major recommendations

- Given the severity of the reported transfusion-associated harm and the lack of evidence of benefit for the liberal transfusion thresholds, we recommend the use of restrictive platelet transfusion thresholds in neonates (see **Box 1**).

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DISCLOSURE

S.J. Stanworth and S.F. Fustolo-Gunnink were involved in the PlaNeT-2/MATISSE trial and STEP survey. H. van der Staaij has nothing to disclose.

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