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REVIEW ARTICLE

TRANSFUSION

Consensus transfusion guidelines for a large neonatal intensive care network

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1 | INTRODUCTION

Neonates and infants hospitalized in the neonatal intensive care unit (NICU) frequently require blood product transfusions, but clinical practices vary widely. Many very low birth weight (VLBW) infants receive packed red blood cell (RBC) or platelet transfusions during their initial NICU stay, with incidence inversely proportional to gestational age at birth.[1,2] A recent study estimated that in infants less than 27 weeks gestation, 70% received RBCs, 34% received platelets, and 24% received plasma to promote coagulation during their NICU admission.[3–5] These blood product transfusions are most often prophylactic, with clinical decisions made in response to numeric blood count values, as opposed to therapeutic transfusions in the context of active bleeding.

Emerging evidence has suggested that some transfusion practices are harmful for certain NICU patients, such as platelet transfusions in preterm infants.[6,7] More broadly, transfusion reactions can occur with virtually all blood products.[8] Although rare in the neonatal population,[9] these reactions may be under-diagnosed, under-estimated, and under-reported in pediatric patients[3] and some papers report that rates may be higher than in adult populations.[9] Our intention was to establish optimal transfusion guidelines for our division and neonatal intensive care network, including 19 hospitals, based on a review of currently available literature. The terms "neonates" and "infants" are used throughout this manuscript to describe any patients hospitalized in the NICU.

Abbreviations: AOP, Apnea of prematurity; aPTT, Activated partial thromboplastin time; BPD, Bronchopulmonary dysplasia; CP, Cerebral palsy; DIC, Disseminated intravascular coagulation; ECMO, Extracorporeal membrane oxygenation; FiO_2, Fraction of inspired oxygen; GDD, Global developmental delay; HIE, Hypoxic ischemic encephalopathy; IVH, Intraventricular hemorrhage; NDI, Neurodevelopmental impairment; NEC, Necrotizing enterocolitis; NICU, Neonatal intensive care unit; PDA, Patent ductus arteriosus; PlaNet-2, Platelets for Neonatal Transfusion Study 2; PLT, Platelet; PT, Prothrombin time; PVL, Periventricular leukomalacia; RBC, Red blood cell; ROP, Retinopathy of prematurity; VLBW, Very low birth weight.

2 | METHODS

We identified blood product transfusion guidelines as a topic that could be amenable to significant quality improvement within our neonatal intensive care network. The modified Delphi method is a systematic, iterative approach geared toward developing consensus among a group of expert stakeholders.[10,11] This approach can be used to help form consensus in areas with divergent evidence base or when expert opinion is utilized. We used this method to identify and implement opportunities to align our transfusion practices with existing literature to optimize patient outcomes. We first defined the scope and specific aims of this consensus project, and then assigned neonatologists to small groups focused on specific topics. The groups reviewed and graded existing literature, and identified areas where a lack of evidence precluded clear recommendations. Each group developed literature-based guidelines and recommendations, which were shared within the broader neonatal care network.

To assess agreement and consensus opportunities based on these guidelines, we posed questions to our neonatal care network providers. We inferred consensus when answers exceeded 7 on a Likert scale of 1 through 9 (1 being least likely and 9 being most likely). Our final consensus guidelines were presented to our Division of Neonatology in an open question-and-answer period. Agreement was sought, at times with live polling during the presentation. Following the larger group discussion, we edited our guidelines and distributed our finalized consensus guidelines among all network sites. We then assessed implementation of these guidelines and perspectives across our network 6 months after finalization.

3 | PLATELET TRANSFUSIONS

Platelets facilitate hemostasis and have important roles in inflammation, immunity, and vascular biology.[12] Thrombocytopenia, defined as a platelet count less than 150,000 platelets/μL blood, most often occurs secondary to infection or other systemic pathology in NICU patients.[13] Platelet transfusions are given most frequently to prevent major bleeding in thrombocytopenic patients, rather than in response to active bleeding.[14] VLBW neonates are at increased risk for thrombocytopenia and are frequently transfused with platelets in the first 7 days of life.[15]

Platelet transfusion practices vary widely. Historically, clinical decision-making has been driven by concerns of increased risk of intraventricular hemorrhage (IVH) or other forms of major bleeding in thrombocytopenic infants. Platelet transfusion thresholds vary by country and institution, but have often been ~50,000/μL or higher for patients with critical illness.[15] While most studies have refuted a correlation between thrombocytopenia severity and risk of IVH,[15] at least one cohort study demonstrated increased IVH with lower platelet count nadirs.[16] The majority of neonates with severe thrombocytopenia (platelet count <50,000 platelets/μL blood) do not have any episodes of major hemorrhage (e.g., Grade 3 or 4 IVH, pulmonary hemorrhage, or abdominal hemorrhage),[14] and most neonates with significant IVH had bleeding prior to developing severe thrombocytopenia.

Several trials have investigated appropriate platelet transfusion thresholds in NICU patients.[6,17,18] Most recently, the Platelets for Neonatal Transfusion Study 2 (PlaNeT-2) was a randomized controlled trial that found a significantly higher risk of death or major bleeding in neonates transfused at a higher threshold (50,000 platelets/μL) than those transfused at a lower threshold (25,000 platelets/μL).[6] The higher transfusion threshold group also had an increased risk of developing bronchopulmonary dysplasia (BPD) and a lower probability of discharge home by 38 weeks corrected gestational age.[6] These effects persisted regardless of patient bleeding or mortality risk stratification.[7] At 2-year follow-up, those randomized to higher transfusion thresholds were at increased risk for the composite rate of death and neurodevelopmental impairment (NDI), as defined by cerebral palsy (CP), global developmental delay (GDD), hearing impairment, or vision impairment.[19] Patients in the high threshold group also had increased risk of requiring oxygen or respiratory support at 2 years of age.[19] These findings support lower platelet transfusion thresholds (~25,000 platelets/μL) for NICU patients regardless of perceived bleeding risk.

When a prophylactic platelet transfusion threshold of 25,000/μL was implemented in a tertiary and quaternary referral center NICU, platelet transfusions decreased overall.[1] The biggest reduction in platelet transfusions was noted in non-bleeding, critically ill neonates. Importantly, there was no change in the incidence of IVH and a significant decrease in other major bleeding complications after the lower platelet transfusion threshold was introduced.

Platelet transfusion dosing recommendations were also considered. Prior work has demonstrated no differences in efficacy between 10 and 15 mL/kg platelet transfusions.[20–22] Several neonatal studies routinely administered 15 mL/kg platelets, including recent large clinical trials.[6] However, concerns have been raised about the potential detrimental effects of this dose on neonatal physiology.[12] A recent quality improvement effort demonstrated efficacy of 10 mL/kg platelet transfusions over 2 h with no change in major bleeding occurrence.[1]

TABLE 1 Platelet transfusion guidelines. We recommend discussing platelet (PLT) transfusion thresholds with consulting hematologists in the setting of thrombolysis or therapeutic anticoagulation, as risks and benefits should be considered for individual patients.

Platelet count threshold ($\times 10^6$/mL)	Non bleeding neonate	Bleeding neonate[b]
<25	**Transfuse** (10 mL/kg over 2 h)	**Transfuse** (10 mL/kg over 2 h)
25–50	Stable—No transfusion ***Consider Transfusion*** if • Critically ill <1000 gram and <1 week old[a] • Hemodynamically unstable • Previous major bleeding <1 week old[b] • Concurrent abnormal coagulation studies • Within 72 pre/post-invasive procedure (i.e., surgery, LP, IR procedure)	**Transfuse** • Minor bleeding does not require transfusion.[c]
50–100	Do not transfuse	**Transfuse**
>100	Do not transfuse	Do not transfuse

[a]Please use clinical judgment for high-risk patients and consider potential causes of bleeding (e.g., necrotizing enterocolitis as an etiology for gastrointestinal bleeding). Critical Illness is defined as the need for respiratory support of high flow nasal cannula ≥ 4 L and/or $FiO_2 \geq 30\%$, and/or hemodynamic instability.

[b]Grade III or IV IVH, intracranial bleeding or pulmonary hemorrhage (new onset).

[c]Petechia, puncture site oozing, or blood-streaked endotracheal tube secretions do *not* necessarily warrant transfusion. Please use clinical judgment.

In sum, there is no conclusive evidence of benefit for platelet transfusions at currently used thresholds in the prevention of major bleeding.[23] Additionally, there are several pathophysiologic mechanisms by which platelet transfusions could harm NICU patients. Neonatal platelets are distinctly different from adult platelets in terms of reactivity to chemical agonists and in protein content.[12,24] Thus, adult platelet transfusions may disrupt normal hemostatic balance, inflammatory mediators, and/or fluid shifts in otherwise vulnerable neonatal patients.[12] These potentially detrimental effects of platelets are important considerations for clinical decision-making regarding platelet transfusion indication and dosage, although these concerns may be balanced with possible benefits of transfusions given sparse evidence overall.

We modeled our platelet transfusion guidelines on recent landmark studies and consensus guidelines used successfully by other institutions, distinguishing between bleeding and non-bleeding neonates and including considerations for clinical situations that may warrant higher transfusion thresholds (Table 1). For the non-bleeding neonate, we recommend platelet transfusion when the platelet count is <25,000/μL, with exceptions (Table 1). For the bleeding neonate, we recommend platelet transfusion if the platelet count is <50,000–100,000/μL. If the platelet count is >100,000/μL, the patient should be evaluated for other potential causes of bleeding.

4 | RED BLOOD CELL TRANSFUSIONS

Anemia of prematurity, transient erythroblastopenia of childhood (reticulocytopenia seen with the physiologic nadir), and iatrogenic blood loss are common etiologies prompting red blood cell (RBC) transfusions in NICU patients. A majority of infants born extremely prematurely are given RBC transfusions during their initial NICU stay.[25] As with platelet transfusions, packed RBC transfusion practices vary widely across hospitals and even between physicians at the same institution. Indeed, we identified practice variations within our own network at the inception of this study.

Several investigations have compared how liberal vs restrictive RBC transfusion thresholds impact clinical outcomes in NICU patients, which have varied among studies.[26–29] Virtually, all studies found a significant decrease in RBC transfusions in the restrictive transfusion groups, in which lower hemoglobin levels were well tolerated.[26,27,29] Despite administering fewer transfusions, there were only subtle differences in blood donor exposure since patients often received RBC aliquots from the same donor unit. One study showed no difference in donor exposures,[26] while another identified fewer donor exposures in the restrictive transfusion group.[29] In general, these studies have found that lower hemoglobin does not adversely impact complications of prematurity, including risks of IVH, periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), apnea of prematurity (AOP), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intestinal perforation, culture-proven sepsis, clinical sepsis, pneumonia, or poor growth. When IVH, PVL, ROP, BPD, time on a ventilator, time on supplemental oxygen, time to regain birth weight, time to double birth

TABLE 2 Red blood cell transfusion guidelines. These pre-transfusion thresholds act as indications for transfusion. Critical Illness is defined as the need for respiratory support of high flow nasal cannula ≥4 L and/or FiO_2 ≥30%, and/or hemodynamic instability. The recommended transfusion volume is 15–20 mL/kg, though discretion of the provider should be used. Feedings should continue at pre-transfusion volumes during transfusion.

	Hemoglobin (g/dL) / hematocrit (%) thresholds	
Week of life	**Critical illness**	**No critical illness**
1	11/32	10/29.5
2	10/29.5	8.5/25
>/= 3	8.5/25	7/21

weight, weight at 36 weeks postmenstrual age, and length of stay were evaluated separately, there was no significant difference in the liberal or restrictive transfusion groups.[26–29] However, one study reported an increase in combined Grade 4 IVH and PVL outcome, and increased apneic events per day in the restrictive group.[26] These differences were not observed in more recent studies, nor were there detectable differences in time requiring caffeine.[27,28] Outcomes at 18- and 24-months corrected age did not differ with regard to death and/or NDI between liberal and restrictive transfusion threshold groups.[27,28,30] Together, these landmark studies support restrictive transfusion thresholds as being safe for NICU patients. It is possible that limitations and imprecision of using hemoglobin level as a proxy for tissue oxygen delivery can, at least in part, explain these observations. Our transfusion guidelines are based on thresholds reported in the most recent report by Kirpalani et al.,[27] and includes stratification by critical vs non-critical illness as defined by being on ≥4 L high flow nasal cannula (HFNC) for respiratory support and the week of life (Table 2).

There has been variation in RBC transfusion dosing among prior studies. Most trials administered 15 mL/kg RBCs per transfusion,[26,27,29] but at least one recent trial provided 20 mL/kg RBCs.[28] Based on these trials, our consensus guidelines recommend transfusion volumes of 15–20 mL/kg (Table 2). Attention to potential circulatory overload may be prudent when transfusing higher volumes. Lower transfusion volumes (10–15 mL/kg) can also be recommended at the discretion of the neonatologist. We administer all transfusions within the expiration period, which is up to 4 h.

Blood supplies, additive solutions, and handling procedures vary across hospitals and hospital systems. While we cannot comment on particular additive solutions herein, we have found that most blood suppliers leukoreduce blood products pre-storage and that many pediatric institutions employ universal irradiation strategies. Our neonatal care network provides irradiated and leukoreduced products for all RBC transfusions.

5 | TRANSFUSION-ASSOCIATED NEC

While RBC transfusions are necessary for many preterm neonates, numerous studies have investigated potential adverse consequences on neonatal physiology and disease pathogenesis.[31–36] These concerns have largely centered on NEC, and clinical controversy continues to prompt prospective clinical studies in addition to publications spanning decades.

One specific clinical concern is that RBC transfusions may lead to mesenteric ischemia, putting neonates at increased risk for NEC 48 to 72 h following a blood transfusion. While some studies have argued against changes in splanchnic oxygenation during RBC transfusions, this remains a matter of debate.[31] Some clinicians have attempted to mitigate intestinal risks by withholding feeds during RBC transfusions. While studies comparing the incidence of transfusion-associated NEC before and after implementing policies to withhold feeding during and after RBC transfusions have shown a trend toward increased NEC risk, none of the studies individually reached statistical significance.[32,33] Although severe anemia may predispose to NEC,[34–36] there has not been clear evidence linking RBC transfusions to an increased incidence of NEC (e.g., transfusion-associated NEC). Thus, there is insufficient evidence at this time to recommend withholding feeds during RBC transfusions, although ongoing trials aim to further evaluate this subject.[37] For further information about the Wheat trial, readers are directed to NCT05213806.[37]

We surveyed our neonatal network providers to assess current practices ($n = 102$ respondents). We found that 28% of responding clinicians currently hold feeds during RBC transfusions, despite widespread opinion for a lack of strong evidence supporting this practice (88%). Of individuals who currently hold feeds during RBC transfusions, 76% reported a willingness to change practice based on updated guidelines and current literature. Of those who already continue enteral feeds during RBC transfusions, 77% offer full volume feeds or continue feeds at pre-transfusion rates. Most respondents (82%) did not consider the degree of anemia when deciding on feeding practices during RBC transfusion. Given the lack of strong evidence supporting transfusion associated NEC, our guidelines recommend continuing feeds at pre-transfusion rates during and after RBC transfusions (Table 2).

6 | PLASMA AND CRYOPRECIPITATE TRANSFUSIONS

Plasma contains coagulation factors and is typically indicated for bleeding with a coagulopathy. There have not been randomized controlled trials to directly evaluate the efficacy of plasma, coagulopathy, and bleeding risk in neonates.[4] Nonetheless, neonates (particularly those born at <34 weeks gestation and critically ill) are given plasma more frequently than other pediatric patient groups.[3] Neonatal plasma transfusions are often given prophylactically for abnormal laboratory values in patients without bleeding.[3,4] Indeed, a retrospective analysis found that approximately half of all neonatal plasma transfusions were administered empirically for abnormal coagulation studies without hemorrhage.[38] It is important to note the paucity of evidence to support prophylactic plasma transfusions for coagulopathy without active bleeding. Prophylactic plasma transfusion also does not prevent future episodes of hemorrhage.[3]

Over the past 15 years, there has been a substantial decrease in neonatal plasma transfusions for abnormal coagulation laboratory tests without a concomitant change major bleeding.[38] In the same time period, studies have shown no benefits for plasma administration in several clinical contexts. For example, infants receiving plasma in the setting of disseminated intravascular coagulation (DIC) had similar outcomes to patients not receiving any treatment.[39] Similarly, there were no differences in short term outcomes, including immunologic responses to sepsis, following plasma administration in non-bleeding patients.[40] Taken together, these findings offer reassurance that limited use of plasma transfusions in neonates is not associated with increased bleeding.

Perhaps most concerning are studies associating plasma transfusions with harm, including increased risks of pulmonary hemorrhage and venous thrombosis,[3] increased mortality,[41,42] or no benefit.[43] One study reported an increase in IVH in infants who received at least one plasma transfusion (although these results did not meet statistical significance).[44] Plasma transfusions in older children have been independently associated with organ dysfunction, infection, and prolonged length of hospitalization.[8]

Administration of 10–15 mL/kg of plasma might be expected to raise coagulation factors by 10%–15%.[3,4,8] However, studies have shown inconsistent effects on coagulation studies following plasma transfusion, with some reporting no change in coagulation testing.[3] This may be due to differences in the hemostatic systems of neonates versus older children.[45]

While we recommend against routine evaluation of coagulation studies in neonates, interpreting these results requires consideration of both gestational and postnatal age. Normal coagulation test values change rapidly in the neonatal period and are dependent on gestational age at delivery.[46] Laboratory thresholds for coagulopathy would be PT and/or aPTT levels elevated to >2× normal references for age.[46]

TABLE 3 Plasma and cryoprecipitate transfusion guidelines.

- Recommend against routine evaluation of coagulation studies in neonates
- Recommend against using plasma or cryoprecipitate for repletion of intravascular volume.
- Consider plasma (5–10 mL/kg over 1 h) for at-risk neonates with signs/symptoms of bleeding.
- Consider cryoprecipitate (5–10 mL/kg over 1 h) for at-risk neonates with signs/symptoms of bleeding and low fibrinogen (<100 mg/dL).
- At-risk neonates include those with active bleeding or uncontrolled oozing, hypoxic ischemic encephalopathy (HIE) undergoing therapeutic hypothermia with bleeding or oozing, and pre-surgical neonates with active bleeding.

We developed guidelines based on judicious use of 5–10 mL/kg plasma over 1 h that align with current expert opinion to transfuse patients with active bleeding, or prior to invasive procedures in coagulopathic patients likely to experience bleeding (Table 3). We defined such at-risk neonates as (1) neonates with active bleeding or uncontrolled oozing, (2) neonates with hypoxic–ischemic encephalopathy undergoing therapeutic hypothermia with bleeding or oozing, and (3) presurgical neonates with active bleeding. We recommend against empiric transfusions in response to abnormal laboratory values without bleeding or coagulopathy prior to invasive procedures. If coagulation studies are obtained, we recommend basing clinical decisions to transfuse plasma for at-risk neonates in the absence of bleeding only if studies are >2× normal values for age.

Several retrospective studies also identified plasma administration in response to clinical concern for hypovolemia or hypotension in neonates, as opposed to specific concerns for coagulopathy.[3] This practice is concerning, since plasma is a blood product with adverse transfusion reaction risks. Plasma is not indicated for volume expansion and we recommend against its use for this purpose (Table 3). To address volume expansion or resuscitation, we recommend isotonic crystalloid infusions. Isotonic fluids are superior to hypotonic fluids in preventing hyponatremia, with customized fluid solutions superior in preventing electrolyte disturbances in pediatric patients.[47] Colloid fluids (e.g., 5% albumin—another blood derived product) have not shown superiority to crystalloids.[47]

Cryoprecipitate is a concentrated plasma derivative rich in factor VIII, XIII, von Willebrand Factor, fibronectin and fibrinogen. Cryoprecipitate can be used in neonates for bleeding, typically in the setting of a low fibrinogen level. Each bag of cryoprecipitate is 15 to 20 mL and contains 100 to 250 mg of fibrinogen, although this may significantly understate the fibrinogen concentration.[48,49] Pediatric dosing of cryoprecipitate is 1 to 2 bags per 10 kg of body weight to raise the fibrinogen level 60–100 mg/dL. For infants, a single unit of cryoprecipitate is a standard dose to achieve hemostasis which is equivalent to approximately 5 to 10 mL/kg.[50] While there is insufficient evidence to recommend therapeutic or prophylactic cryoprecipitate transfusions in neonates and infants, our clinical guidelines outline the potential use of 5 mL/kg transfusions in actively bleeding patients with low fibrinogen or active therapeutic thrombolysis as clinically warranted[4] (Table 3). While some products may be subject to supplier restrictions, these issues are often hospital-specific and outside the scope of this current recommendation.

7 | CONCLUSION

Neonates and infants are vulnerable patient populations and emerging studies have shown evidence for harm associated with some current blood product transfusion practices.[3,6,8,17,18] Recent trials described herein have refined evidence-based practice for blood product transfusions in neonates. We developed transfusion guidelines for neonates and infants based on current evidence and implemented these network-wide to improve transfusion practice and safety. We surveyed providers across our 19-hospital neonatal network 6 months after finalizing the guidelines. We received 72 completed responses. We found that 89% of respondents were familiar with the new guidelines and stated they were following them, with 57% reporting a change in transfusion practices. On the survey, the most frequent changes were to transfuse at more restrictive thresholds, continuing feeds during transfusions, and transfusing lower volumes of platelets. Half of respondents (50%) stated they had a change in mindset toward transfusions, including anecdotal comments reflecting providers no longer believed transfusions to be benign, and that providers were more restrictive in transfusion administration in accordance with the guidelines.

We anticipate that future trials will further clarify recommendations for specific at-risk patient populations (e.g., for extremely premature infant platelet transfusion thresholds, infants on ECMO, or those requiring massive transfusion protocols) to further refine transfusion guidelines that optimize care for neonates and infants.

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CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

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