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Transfusion in the Neonatal Patient: Review of Evidence Based Guidelines

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Summary

Transfusion of red blood cells (RBCs), platelets and fresh frozen plasma (FFP) in neonatal patients has not been well characterized in the literature, with guidelines varying greatly between institutions. However, anemia and thrombocytopenia are highly prevalent especially in preterm neonates. When transfusing the neonatal patient, clinicians must take into consideration physiologic differences, gestational and postnatal age, congenital disorders, and maternal factors while weighing the risks and benefits of transfusion. This review of existing literature will summarize current evidence-based neonatal transfusion guidelines and highlight areas of current ongoing research and those in need of future studies.

Keywords

transfusion medicine; neonate; premature infant; platelet; red blood cell transfusion; fresh frozen plasma

Introduction

Although a critical therapy in the management of hospitalized pediatric patients[1,2], transfusion of red blood cells (RBCs), platelets and fresh frozen plasma (FFP) in neonatal patients has not been well characterized in the literature, with few studies describing the indications and recommendations for transfusion in this unique patient population. Anemia and thrombocytopenia are highly prevalent especially in preterm neonates, with the majority of premature infants in neonatal intensive care units (NICUs) requiring at least one transfusion in the first week of life[3,4].

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Physiologic differences between neonates and older infants and children must be taken into account when considering transfusion of blood products. The neonatal period encompasses the first four weeks after birth (<28 days old) and includes both full term (>39 weeks gestational age) as well as premature infants (any neonate born before 37 completed weeks of gestation). The majority of preterm infants requiring transfusion are very-low-birth-weight (VLBW), weighing <1,500 grams and extremely-low-birth-weight (ELBW), weighing <1,000 grams[5]. When evaluating neonates with anemia, thrombocytopenia, bleeding, or coagulopathy, the clinician should consider gestational and postnatal age, congenital disorders, maternal factors, and transplacental antibody transfer. In addition, neonates have smaller blood volumes relative to larger children or adults, so potentially toxic exposures or antibodies present in transfused products may be more likely to result in clinically relevant consequences[6,7].

Unlike in the more well-studied adult population, guidelines for transfusion in neonates varies greatly worldwide and between institutions[8–11]. More recently, a growing body of research has focused on delineating neonatal transfusion specifics. This review of existing literature will summarize current evidence-based neonatal transfusion guidelines and highlight areas of current ongoing research and those in need of future studies.

Fetal and Neonatal Hematopoiesis

Term neonates—When making the decision to transfuse during the neonatal period, it is important to understand fetal and neonatal hematopoiesis. Hemoglobin concentration increases progressively throughout gestation and peaks after birth. A full-term neonate has a hemoglobin value of 16 to 17 g/dL at term, which may increase by 1 to 2 g/dL due to placental transfusion at birth and may vary depending on timing of cord clamping. There is a gradual decline in hemoglobin concentration to a nadir of 11–12 g/dL at 8 weeks, termed physiologic anemia[12]. Erythropoiesis then accelerates, followed by a rise in hemoglobin.

Premature Neonates—Physiologic anemia can be more pronounced in premature infants, and the decline in hemoglobin may occur earlier. In addition, premature infants often have a marked decrease in hemoglobin concentration, termed anemia of prematurity. Anemia of prematurity is due to a combination of a lower hemoglobin at birth based on gestational age, reduced RBC lifespan, decreased production of endogenous erythropoietin, hypo-regenerative bone marrow, medical complications and frequent blood sampling, all resulting in a limited response to anemia[13].

NEONATAL RED BLOOD CELL TRANSFUSION

RBC transfusion is a critical intervention to increase oxygen carrying capacity in the anemic neonate. In addition to severe anemia, indications of transfusion in the early neonatal period can include acute blood loss, hypotension, hypovolemia or to improve oxygen-carrying capacity in infants with respiratory failure[14]. Although often life-saving, transfusions also have the potential to cause adverse effects including hemolytic transfusion reactions, alloimmunization, infections, volume overload, allergic reactions, or iron excess[15,16]. Therefore, especially in the vulnerable neonatal population, it is essential to establish guidelines to determine when transfusion is indicated.

Strategies to Limit RBC Transfusions in Neonates

Preventive strategies to decrease the incidence of anemia and resultant use of RBC transfusions in neonates have been employed, with variable success.

Limiting Phlebotomy Losses—Phlebotomy-related blood losses can be minimized by alterations in practice, including use of point-of-care devices, minimizing unnecessary laboratory testing, in-line arterial testing, and optimizing frequency and volume of blood draws. In addition, umbilical cord blood can be utilized for neonatal blood type and screen, complete blood count with differential, and blood culture[17]. Although there is a chance that confirmatory testing may be needed due to interference from Wharton's jelly, use of cord blood in initial testing can significantly decrease blood loss due to phlebotomy. Employment of these strategies has been shown to decrease phlebotomy losses and/or the need for RBC transfusion and should be considered, especially in the VLBW premature infant[18].

Delayed Cord Clamping—Delayed cord clamping (≥30 seconds) has recently been utilized to increase the initial hematocrit of neonates at birth. This practice has shown to significantly decrease the number of transfusions needed in neonates and is associated with a lower incidence of intraventricular hemorrhage and acute gut injury as well as a decrease in hospital mortality when compared to immediate cord clamping[19–23]. However, delayed cord clamping has not been well-studied in the group of neonates who most often require transfusion, VLBW neonates. This high-quality evidence supports current guidelines from the American College of Obstetricians and Gynecologists (ACOG) recommending delayed cord clamping in premature infants[20,22].

Pharmacologic Interventions—Recombinant human erythropoietin (EPO) has been used in an attempt to diminish the severity of or to treat anemia of prematurity as well as to decrease the need for RBC transfusion in premature neonates. While EPO has been shown to effectively stimulate erythropoiesis in premature infants, initial studies were conflicting in demonstrating a reduction in the need for RBC transfusion or on improvement in overall neurologic outcome[24–28]. Ohls, *et al* reported that administration of darbepoetin or EPO to premature infants resulted in both a decreased number and volume of transfusions[26] as well as improved cognitive outcome at 18–22 months[27]. In contrast, a multicenter randomized controlled trial (PENUT trial) in 2020 found no significant difference in the incidence of death or severe neurodevelopmental impairment at 2 years of age in 741 extremely premature infants that were randomized to receive placebo or high-dose EPO[28]. However, a post-hoc analysis reported that infants receiving EPO required transfusion of a significantly decreased volume of RBCs after 10 days of life compared to placebo[29]. Therefore, particularly as patient blood management strategies are critical, EPO is being considered to decrease the need for RBC transfusion in premature infants.

Further contributing to anemia, premature infants have a relative deficiency in iron stores as a result of incomplete iron transport from the mother to the fetus prior to birth[30]. The use of iron supplementation has been shown to slightly increase the hemoglobin level in premature and low birth weight infants, while improving overall iron stores and decreasing the risk of developing iron deficiency anemia[31]. Of note, a study of VLBW infants demonstrated

that both higher cumulative dose of enteral iron supplementation and total volume of RBCs transfused were independently associated with the development of bronchopulmonary dysplasia (BPD)[32]. The optimal dosing and timing of iron supplementation as well as mechanisms underlying the association remains to be studied.

Potential Risks of RBC Transfusion in the Neonate

Determining the optimal hemoglobin concentration at which transfusion is indicated is imperative in premature infants due to their higher likelihood of requiring transfusion resulting from lower hemoglobin levels at birth, iatrogenic losses from phlebotomy and anemia of prematurity. Although RBC transfusions can be life-saving for neonates with severe anemia or bleeding, there are inherent risks associated with transfusion that must be considered. Additionally, RBC transfusion continues to be studied to determine potential contribution to some of the major causes of morbidity and mortality in preterm infants, including necrotizing enterocolitis (NEC), BPD, intraventricular hemorrhage (IVH), or death[33–35]. Conversely, some studies have raised concerns regarding risks associated with delaying transfusion and allowing more permissive levels of anemia in preterm infants[36].

RBC Transfusion and Necrotizing Enterocolitis—NEC is a devastating disease in neonates, accounting for 1 in 10 deaths in United States NICUs[37]. The etiology of NEC remains incompletely understood and further delineating the underlying risk factors remains an important area of research. Although previous data have been conflicting[38], a recent study showed that among VLBW infants, severe anemia (≤8 g/dL), but not RBC transfusion was associated with an increased risk of NEC[39]. Additionally, it was also noted that anemic infants were at higher risk of developing NEC than infants with normal hemoglobin concentrations[36]. This is further supported by previous studies suggesting that immune dysregulation underlies NEC development[40–43], combined with recent studies demonstrating an increase in the proinflammatory cytokine interferon gamma in VLBW preterm infants with anemia, suggesting this may predispose them to the development of NEC[44].

Neurologic Outcome in Premature Neonates—Of particular importance in preterm infants is the development of neuroprotective strategies to improve overall outcome. Large periventricular hemorrhagic infarctions in neonates are associated with poor neurodevelopmental outcomes, and are more likely to occur with wide fluctuations in blood pressure and blood flow through the delicate capillary beds in premature infants[45]. Previous studies have suggested an association between IVH in VLBW infants and transfusions administered during the first few days following delivery[8,46,47]. However, the development of IVH in preterm neonates is certainly multi-factorial[48]. Regardless, children born preterm, and especially those that are VLBW, are at higher risk of long-term neurologic sequelae than term infants, including major impairments such as cerebral palsy, intellectual disability, deafness, or blindness[49,50] as well as behavioral and psychiatric disorders[51–53]. Therefore, it is essential to identify evidence-based transfusion practices in order to define the benefits and risks associated with RBC transfusion, especially in this neurologically vulnerable premature population of infants.

Optimal RBC Transfusion Thresholds in Neonates

Two previous large randomized controlled trials (RCTs) aiming to define neonatal RBC transfusion thresholds reported conflicting results regarding neurocognitive outcomes in preterm neonates receiving liberal compared to restrictive transfusion thresholds[54,55]. This important issue has been reexamined recently with two additional RCTs, with the goal of providing evidence-based recommendations for clinicians (Table 1).

The Effect of Transfusion Thresholds on Neurocognitive Outcomes (ETTNO) Trial—Results from the Effect of Transfusion Thresholds on Neurocognitive Outcomes of extremely low birth weight infants (ETTNO) trial have recently been published[56]. This RCT, conducted in 36 NICUs in Europe, enrolled ELBW infants who were randomized to receive RBC transfusion based on liberal (Hct 34–41% in critical and 28–35% in non-critical infants) versus restrictive (Hct 27–34% in critical and 21–28% in non-critical infants) RBC transfusion thresholds. In addition to current state of health, the hematocrit trigger thresholds of each group were assigned based on postnatal age (<7 days, 8–21 days, or >21 days old). The primary outcome of death or disability (defined as cognitive deficit, cerebral palsy, or severe visual or hearing impairment) at 24 months corrected age did not differ between neonates randomized to liberal or restrictive transfusion groups.

The Transfusion of Prematures (TOP) Trial—The Transfusion of Prematures (TOP) trial is a multi-center study in the United States sponsored by the National Institute of Child Health and Human Development (NCT01702805). It randomizes ELBW infants with gestational age <29 weeks to receive RBC transfusion based on a liberal (Hct 32–38% in infants receiving respiratory support and 29–35% in infants without respiratory support) or restrictive (Hct 25–32% in infants receiving respiratory support and 21–29% in infants without respiratory support) hemoglobin thresholds. Similar to the ETTNO trial, different thresholds were used based on postnatal age. The primary outcome was survival and rates of neurodevelopmental impairment at 22–26 months corrected age. Preliminary findings in a recently presented abstract agreed with the findings in the ETTNO trial, demonstrating no difference between infants in the liberal vs restrictive groups[57].

Limitations to ETTNO and TOP Trials—The vast heterogeneity of critically ill patients contributes to the difficulty in interpretating the results of clinical trials. An important caveat of both the ETTNO and TOP trials is that neonates were not randomized to the most restrictive hematocrit levels until they were older than 21 days. Instead, during the first 2 weeks of life, less restrictive thresholds were used. Additionally, the restrictive level of ~Hb 8–10 or higher if the infant was critically ill or receiving respiratory support is still higher than the usual restrictive levels used at most institutions for pediatric patients. Thus, although the studies did not observe a difference in primary outcome between the restrictive and liberal transfusion groups, an important question that remains to be determined is whether early anemia and/or prolonged anemia results in potential detrimental effects. Future studies are needed to fully inform clinicians on the proper transfusion support parameters for neonates to achieve the best ultimate outcome.

Also, of note, the above neonatal transfusion trials function to compare liberal versus restrictive transfusion strategies based on laboratory thresholds alone (hemoglobin or hematocrit). However, cell count alone may not be an accurate predictor of physiologically relevant outcomes such as tissue oxygen delivery[58], especially in neonates with varying levels of illness, age and gestational age. Studies are needed to identify more all-inclusive markers of clinical outcome as well as including long term outcomes due to the immunomodulatory effects of transfusion that may have effects on neurodevelopment, immunity, and inflammation.

RBC Product Selection for Neonates

Once the decision has been made to transfuse RBCs, the most appropriate product must be chosen. There is little guidance available regarding appropriate blood product collection, storage, and pathogen testing in the neonatal population. These topics are covered in more detail in Chapter 5: Inventory Management and Product Selection in Pediatric Blood Banking.

Special considerations in the neonatal patient include ABO compatibility, total blood volume, immaturity, immunosuppression, immunodeficiencies, and blood donor exposure. Factors to consider when choosing type of RBC product to administer to a premature infant or neonate include type of anticoagulant-preservative solution (CPDA-1 vs. additive solutions – AS-1, AS-3, etc)[59], potassium load which varies depending on the unit storage length, and risk of citrate toxicity. Generally, specific RBC product selection recommendations for neonates are not necessary when *small*-volume transfusions (i.e. < 20 mlmL/kg of RBCs) are administered.

Fresh vs stored RBCs—A recent RCT demonstrated no difference in outcome when utilizing fresh (≤7 days) versus standard-issue RBCs in premature very-low-birth-weight infants[60]. Accordingly, the clinical practice guidelines from the AABB recommend that standard-issue RBC units are administered to neonates rather than limiting to transfusion of fresh (<10 days) RBC units[61].

When *large*-volume transfusions are required, such as in cases of hypotensive shock, extracorporeal membrane oxygenation (ECMO), exchange transfusion, or cardiopulmonary bypass, there is a risk of elevations in plasma potassium from stored units. In this situation, it may be prudent to consider fresher, washed, or volume-reduced RBCs which all have lower potassium loads[62,63]. Additionally, calcium levels should be closely monitored in the neonate requiring multiple transfusions due to the risk of citrate toxicity and resultant hypocalcemia.

ABO Group and Antibody Screen—During pregnancy, transplacental transfer of maternal immunoglobulin G (IgG) antibodies to the fetus can occur, and this can include anti-RBC antibodies. With maternofetal hemorrhage, immunoglobulin M (IgM) antibodies may be transferred. Therefore, when selecting RBC units for transfusion in the neonate, they must be compatible with both the neonatal blood type as well as any maternal antibodies present. Due to this, many institutions will transfuse group O RBCs to all neonates, however,

ABO-specific blood can be transfused if tests determine there are no anti-A, anti-B or anti-A,B IgM or IgG maternal antibodies present directed towards the neonate's RBCs[64].

When performing an antibody screen prior to transfusion of a neonate, maternal blood can serve as the source as any antibodies present originated in the mother. A negative initial antibody screen in a neonate does not need to be repeated during a hospitalization until 4 months of age[64], as the immature immune system of a neonate rarely produces antibodies in response to RBC transfusion. If an antibody is detected, antigen-negative units should be provided until it has been determined that the antibody has cleared from the infant's circulation.

Limiting donor exposure—Many institutions attempt to limit donor exposure by reserving specific units for neonates, and retrieving sterile docked aliquots for transfusion to be drawn off as needed until outdate of the unit[5,65,66]. Transfusion of aliquots from the same donor in instances where multiple transfusions are required can minimize potential risks that can be associated with transfusion of blood components from multiple donors.

Cytomegalovirus transmission in neonates—Of specific interest in the developing neonate is mitigating the risks of transfusion-transmitted (TT) infections with known clinical complications in this vulnerable population. In addition to other groups of immunocompromised patients, premature neonates are a high-risk group for severe disseminated infection from cytomegalovirus (CMV). During latent CMV infection, the virus is associated with mononuclear leukocytes, therefore, leukocyte reduction decreases the risk of TT-CMV[67–71]. A small number of clinical trials have estimated the risk of acquiring CMV from leukocyte reduced blood to be well below 1%[67–72]. Although small, there remains a risk of asymptomatic CMV-seronegative donors in early stages of infection transmitting CMV through virus particles in plasma[73,74].

A prospective study of VLBW infants reported no CMV infection after transfusion of 2081 blood products that were both leukocyte reduced and CMV seronegative[75]. Furthermore, a prospective observational study did not find any cases of TT-CMV in VLBW infants who received either leukocyte reduced blood products or both leukocyte reduced and CMV seronegative products[76]. Notably, most neonatal CMV cases result from transmission from the mother most often by maternal breast milk rather than transfused blood products. Therefore, it is reasonable to assume that leukocyte reduced blood components reduces the risk of TT-CMV to that similar to CMV-negative products without window period breakthrough.

In light of the above evidence, a reasonable approach is administration of blood products with reduced risk of CMV transmission (CMV-seronegative if available or leukocyte reduced) to premature neonates with a birth weight of <1500g prior to their initial discharge home. Future studies should focus on the efficacy and safety of pathogen inactivation approaches in neonates, especially on extremely preterm neonates.

NEONATAL PLATELET TRANSFUSION

Thrombocytopenia in the Neonate

Thrombocytopenia is common in the neonate, and can affect an estimated 1–2% of otherwise healthy newborns. Critically ill neonates have an even higher rate of thrombocytopenia with 20–35% having platelets counts of <150,000/μL[77]. The incidence increases with decreasing gestational age with approximately 70% of VLBW neonates experiencing thrombocytopenia[77,78]. The differential diagnosis of thrombocytopenia in neonates is broad, and includes intrauterine infection, placental insufficiency, neonatal sepsis, drugs, and immune thrombocytopenia[79]. Approximately 20–25% of affected neonates receive at least one platelet transfusion[78,80], which is administed in the majority of cases not for bleeding, but when the platelet counts reaches an arbitrary threshold[10,80].

The incidence of bleeding in neonates increases with decreasing gestational age, with a prospective observational study showing a 63% incidence of bleeding in infants <28 weeks gestation compared to 14% in infants >28 weeks gestation[81]. The most severe bleeding complication in neonates is IVH, which, when present, has the potential to affect long-term neurodevelopmental outcomes[10]. However, the risk of bleeding in neonates is not correlated well with overall platelet counts, making it difficult to determine the proper threshold at which transfusions should be administered[81].

Physiologic Differences Between Neonatal and Adult Platelets

Platelet function and risk of bleeding is challenging to assess in the neonate, as neonatal platelets are hyporeactive to several of the agonists used to test function in the laboratory. Despite this, tests of primary hemostasis are normal or even show shorter bleeding and closure times than adults[82,83]. This is in part, due to other differences including higher hematocrits and increased von Willebrand factor concentrations in neonates. Ongoing studies focused on the development of tools to evaluate platelet function and whole blood hemostasis in an individual neonate may be able to more specifically address the need for a platelet transfusion[84]. These differences between the neonatal and adult hemostatic system should be kept in mind when considering transfusion of platelets, and when determining thresholds for transfusion.

Platelet Transfusion Thresholds in the Neonate

The goal of prophylactic platelet transfusion is bleeding prevention, however a neonate's platelet count and bleeding risk are not directly correlated[85]. Moreover, platelet transfusions are not without risk[86]. Data is limited, but much improved recently with newer studies, to guide platelet transfusion in preterm and more mature neonates, due to limited clinical trials in this patient population[87]. However, there have been some recent advances contributing to platelet transfusion strategies in the premature neonate, with three recently completed RCTs (Table 2).

A large RCT, performed over 30 years ago, found there was no increase in the development of new intracranial hemorrhage (ICH) or worsening of existing ICH when premature thrombocytopenic infants were randomized to receive platelet transfusions at thresholds of

either 50,000 or 150,000/μL. The study did conclude that there was a decreased use of FFP and RBC transfusions when transfusing platelets at a higher threshold[88]. However, the lower threshold in the study (50,000/μL) is significantly higher than that used commonly in current clinical practice.

Most recently in 2019, the PlaNeT-2 RCT compared two different platelet transfusion thresholds (25,000/μL versus 50,000/μL) in premature infants born at <34 weeks gestational age[89]. They reported a significantly higher incidence of death or major bleeding in the group of neonates receiving platelet transfusion with a threshold of 50,000/μL compared to those randomized to receive transfusion at a threshold of 25,000/μL. Moreover, there was also a higher incidence of BPD in the higher threshold group, further supporting the use of a more restrictive transfusion threshold in premature infants.

A sub analysis of the PlaNeT-2 trial more closely examined the risk of major bleeding or death in the lowest and highest risk infants included in the trial. Regardless of risk category, neonates had a better outcome when a lower platelet count threshold was used, with the highest risk infants gaining the greatest benefit[86]. Additional studies have provided further evidence to support lower platelet transfusion thresholds in nonbleeding premature neonates[85,90,91].

A third recent RCT reported there was no effect of platelet transfusion threshold (100,000/μL vs 20,000/μL) on time to closure of patent ductus arteriosus (PDA) in premature neonates[92]. However, they did note more cases of IVH among the infants receiving platelet transfusions to keep platelet count >100,000/μL.

Limitations of Previous Platelet Threshold Trials—These studies support the implementation of a restrictive platelet transfusion guideline in premature infants. However, premature neonates included in these studies were of a wide postnatal and gestational age. In addition, the clinical status of a neonate should be considered in order to determine the proper platelet threshold. A study investigating full term neonates is needed, as is one examining VLBW premature infants and the most critically ill neonates to more clearly define the effect of lower thresholds during the first week of life and the highest risk period of bleeding[93].

Current Neonatal Platelet Transfusion Recommendations—With the currently available studies, a reasonable approach for VLBW infants would be to transfuse for platelet levels <25,000/μL if not bleeding, more than 7 days old, and not having a procedure in the next 24 hours. For other groups of neonates, the platelet transfusion threshold should take into account the patient's clinical severity and risk of bleeding, as well as risk of other comorbidities that may be associated with platelet transfusion. In general, platelet transfusions are indicated when there is significant thrombocytopenia with active bleeding, or when there is an increased risk of IVH, which is typically defined as a platelet count of <30,000/μL.

Platelet Product Selection in the Neonate

Product selection is covered in great detail in Chapter 5: Inventory Management and Product Selection in Pediatric Blood Banking. However, we will discuss briefly here the issue of ABO-mismatched platelet transfusions in the neonatal population. ABO-compatible or identical platelets are ideally transfused to avoid the transfer of incompatible isohemagglutinins (anti-A, anti-B, or anti-A,B antibodies) found in plasma to the recipients, resulting in potential RBC hemolysis[7,94]. Although uncommon, there are case reports describing morbidity and mortality in neonates and children receiving ABO-incompatible platelet transfusions[7,95–97]. In most cases, O-donor platelets (containing anti-A) have resulted in complications in patients with blood type A. This is of particular concern in neonates, particularly premature and VLBW infants, due to their small plasma volume and inability to dilute out the passive transfer of antibodies following platelet transfusion. Therefore, all attempts should be made to administer ABO-identical or compatible platelet transfusion in this population. However, as it can be difficult to obtain ABO-compatible platelets due to product shortages, alternate, though less ideal strategies include washing or volume reducing ABO-mismatched platelets. Additionally, although further research is needed to determine ideal “safe” antithetical antibody titers, administration of low-titer anti-A platelet units to neonates in these cases would be reasonable[7].

Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT)

Fetal and neonatal alloimmune thrombocytopenia is the result of passively acquired maternal IgG anti-platelet antibodies that cross the placenta and mediate destruction of fetal platelets. The majority of cases of FNAIT are the result of maternal antibodies developing against the paternally inherited platelet antigen human platelet antigen 1a (HPA-1a), but can also include a number of other antigens, with their incidence depending on the mother’s ancestry[98–101].

FNAIT occurs in 1 to 10 per 10,000 live births, with severe thrombocytopenia and ICH occurring in 3 to 10 per 100,000 infants[102–104]. Roughly 40–60% of cases of FNAIT affect a woman’s first pregnancy and ~90% of subsequent pregnancies are affected, with severe disease occurring more often. Severely affected infants have early-onset severe thrombocytopenia and bleeding including petechiae, purpura and mucocutaneous bleeding. There is a 10–20% risk of neonates with platelet counts of <50,000/uL of developing ICH[99].

Although maternal antibodies are cleared within 1–3 weeks, due to the risk of severe bleeding during this time, treatment may be indicated. There is variable evidence of the efficacy of IVIG and corticosteroids in raising the platelet count in neonates affected by NAIT[105,106]. Platelet transfusion may be indicated prophylactically in the first week of life for platelet counts <50,000/μL, with a more restrictive threshold of 30,000/μL often used in stable infants afterwards. A bleeding infant with thrombocytopenia and suspected NAIT should receive transfusion of the most readily available platelet unit without delay. Use of platelets that express the targeted antigen will transiently increase the platelet count, although transfusion of antigen negative platelets or washed and irradiated maternal platelets may be needed[107–110].

NEONATAL PLASMA TRANSFUSION

Plasma transfusion in neonates is often utilized incorrectly[111–116]. This may, in part, be due to the lack of evidenced-based guidelines available to guide transfusion of FFP in the pediatric patient population. It is essential to determine the clinical scenarios in neonates that require transfusion of plasma, and to differentiate those in which an alternate product, such as a specific factor concentrate, should be used. Of note, in the absence of bleeding, plasma should not be transfused empirically, or for an elevated INR alone[112–118]. In addition, plasma is not indicated for volume expansion, and routine and prophylactic use of plasma has not been shown to reduce the mortality of premature infants[119].

Indications for Plasma Transfusion

Although evidence-based guidelines are scarce in the neonatal population, there are a number of clinical conditions in neonates that require the transfusion of plasma. Sepsis, disseminated intravascular coagulopathy, liver disease, congenital or acquired Vitamin K deficiency, trauma or dilutional effects of massive transfusion all have the potential to result in global coagulopathy in the neonate[120–124].

In patients diagnosed with suspected or confirmed congenital thrombotic thrombocytopenic purpura (TTP), therapeutic plasma exchange should be performed with plasma as the replacement fluid to replenish ADAMTS13[125]. Plasma is also used to reconstitute whole blood to be used for neonatal exchange transfusion as well as, in some cases, to prime both cardiothoracic surgery circuits as well as ECMO circuits. However, there is variability between institutions and conflicting data on the best combination of products to utilize when priming circuits[126–131].

Coagulation Factor Deficiencies—It can be difficult to establish a diagnosis of a specific coagulation factor deficiency due to physiologically decreased levels of some coagulation proteins in neonates as a result of the normal development of the coagulation system. For example, most coagulation factors in a neonate (factors II, VII, IX and X, XI and XII) are roughly 50% the adult levels and gradually increase until 6 months of age. Conversely, levels of factors V and XIII and fibrinogen at birth are similar to adult levels, and factor VIII and von Willebrand factor levels rise at birth and remain elevated for the first 6 months[132]. This functional immaturity of the coagulation system can lead to challenges interpreting results and reaching a diagnosis.

Plasma is indicated to replace specific coagulation factors when factor concentrates are not available, particularly Factors V and XI, for which specific factor concentrates are not available in the United States[117,118,133,134]. In addition, if a congenital bleeding disorder is suspected, it is prudent to administer plasma in a bleeding patient while awaiting definitive testing[122].

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Key Points

- Transfusion recommendations in neonatal patient are less defined by evidence-based guidelines than older children and adults.
- When making the decision to transfuse a neonate, the clinician should consider physiologic differences of this age group, gestational and postnatal age, congenital disorders and maternal factors.

Table 1.

Multi-center RCTs comparing liberal versus restrictive RBC transfusion in ELBW infants

Trial	Patient Population	Transfusion Threshold (Hct)	Primary Outcome	Results
Effect of Transfusion Thresholds on Neurocognitive Outcomes (ETTNO) [56]	1,013 premature infants in Europe; GA <30 weeks; BW <1000g	Liberal: 28–41% Restrictive: 21–34% (After randomization, threshold based on postnatal age and health status)	Death or neurodevelopmental impairment at 24 months corrected age	No difference between liberal vs restrictive transfusion; 44.4% vs 42.9% OR 1.05 (95% CI, 0.80–1.39) P=0.72
Transfusion of Prematures (TOP) [57]	1,824 premature infants in the United States; GA 22 to <29 weeks; BW <1000g	Liberal: 32–38% Restrictive: 21–32% (After randomization, threshold based on postnatal age and health status)	Survival, neurodevelopmental impairment at 22–26 months corrected age	Manuscript pending; preliminary results with no difference between liberal vs restrictive transfusion

Abbreviations: RCT, randomized controlled trial; GA, gestational age; BW, birth weight; RBC, red blood cell; ELBW, extremely low birth weight

Table 2.

RCTs comparing liberal versus restricted platelet transfusion in ELBW infants

Trial	Patient Population	Platelet Thresholds	Primary Outcome	Results
Andrew, *et al.*[88]	152 infants; GA <33 weeks; BW 500–1500g; platelet count <150,000/μL during the first 72 hours of life	150,000/μL vs 50,000/μL	Incidence or extension of ICH	No difference in new/worsening ICH between higher and lower threshold (28% vs 26%, P=0.73); higher threshold received less FFP and RBCs
Curley, *et al.* PlaNeT-2 Trial[89]	660 infants; GA <34 weeks; Platelet count <50,000/μL	50,000/μL vs 25,000/μL	Death or new major bleeding	Higher rates of death or major bleeding in higher threshold group; OR, 1.57; 95% CI, 1.06 to 2.32; P=0.02
Kumar, *et al.*[92]	44 infants; GA <35 weeks; PDA detected at <14 days of age; platelet count <100,000/μL	100,000/μL vs 20,000/ μL	Mean time to PDA closure	No significant difference in time to PDA closure; Adjusted HR 1.4 (95% CI 0.57–3.47), P=0.46

Abbreviations: RCT, randomized controlled trial; GA, gestational age; BW, birth weight; ICH, intracranial hemorrhage; OR, odds ratio; CI, confidence interval; PDA, patent ductus arteriosus; HR, hazard ratio