Neonatal and pediatric platelet transfusions: Current concepts and controversies

Ravi Mangal Patel, MD, MSc1, Cassandra Josephson, MD1,2,3
1Department of Pediatrics, Emory University School of Medicine and Children’s Healthcare of Atlanta, Atlanta, GA
2Aflac Cancer Center and Blood Disorders Service, Children’s Healthcare of Atlanta, Atlanta, GA
3Department of Pathology and Laboratory Medicine, Center for Transfusion and Cellular Therapies Emory University School of Medicine, Atlanta, GA

Abstract

Purpose of review: In this review, we focus on three specific concepts related to platelet transfusion in the neonatal and pediatric population: 1) Choice of transfusion threshold; 2) Use of ABO-mismatched platelets; 3) Transfusion of pathogen-reduced or inactivated platelets.

Recent findings: Recent trials support the use of lower platelet transfusion thresholds (25,000/μL) in preterm neonates, although data is limited to guide transfusion among more mature neonates. In children, there is low-level evidence as to what the prophylactic platelet transfusion threshold should be in many situations of thrombocytopenia, revealing major variability in platelet transfusion practices. Most pediatric guidelines are extrapolated from adult studies with the most evidence in treatment-associated hypoproliferative thrombocytopenia varying between a platelet transfusion threshold of 10,000/μL to 20,000/μL. Although pathogen-reduced platelets may lower the risks of transfusion-transmitted infection, the effects on platelet refractoriness and transfusion burden in this population warrant additional study.

Summary: Our review highlights recent advances in neonatal and pediatric platelet transfusion and also emphasizes the urgent need for better evidence to guide practice given recent studies showing the potential harms of platelet transfusion, particularly with liberal use.

Keywords
platelets; thrombocytopenia; blood; bleeding; hemostasis

Introduction

Thrombocytopenia, defined as a platelet count <150,000/μL, is a common problem in the neonatal and pediatric population. Although most neonates and children with thrombocytopenia do not receive platelet transfusion, some will be transfused with platelets...
to treat or prevent bleeding. When deciding whether or not to administer a platelet transfusion, the clinician must decide on the appropriate platelet threshold that will maximize the benefit-to-risk ratio for the patient. In addition, blood banks and clinicians must make choices regarding the optimal platelet product to be transfused. In this review, we summarize recent data on three important and potentially controversial areas of platelet transfusion in the neonatal and pediatric population: 1) Choice of transfusion threshold; 2) Use of ABO-mismatched platelets; 3) Transfusion of pathogen reduced or inactivated platelets. Rather than a comprehensive review, we focus on the most relevant and recent studies to address these three concepts.

**Platelet Thresholds for Transfusion in Neonates**

Bleeding occurs in 25% of neonates and infants in the neonatal intensive care unit setting(1) and thrombocytopenia affects 22% to 35%(2). There is uncertainty regarding the optimal threshold for platelet transfusion to treat or prevent bleeding, with large variation differences in practices(3). Herein, we focus on two specific populations: preterm and term neonates.

**Preterm neonates**—The incidence of platelet transfusion and thrombocytopenia are both inversely related to the gestational age at birth(4, 5), similar to the incidence of severe bleeding. In a prospective observational study of 146 neonates, the incidence of bleeding among infants < 28 weeks’ gestation was 63%, compared to 14% among more mature infants ≥28 weeks’ gestation. Severe intraventricular hemorrhage (IVH) is among the most concerning bleeding, given the impact of its sequelae on long-term neurodevelopmental outcome(3). In a multicenter observational study of very low birth weight (VLBW) infants, 24% of infants received one or more platelet transfusions, with many receiving platelet transfusion at pre-transfusion platelet counts higher than 50,000/μL, despite no association between the severity of thrombocytopenia and risk of IVH(6). Another study showed no clear relationship between platelet count and risk of bleeding among thrombocytopenic infants, in which 91% of infants with a platelet count <20,000/μL did not develop major bleeding(7). These studies suggest that the severity of thrombocytopenia in neonates is not a strong predictor of bleeding risk.

Given the lack of compelling data demonstrating the severity of thrombocytopenia to be a major predictor of bleeding, it is appropriate to question the use of liberal platelet thresholds for prophylactic platelet transfusions. Three prior trials in preterm infants have compared higher vs. lower platelet thresholds (Table 1). Andrew et al. published the first trial comparing prophylactic platelet transfusion in the first week of life and found no difference in the risk of new intracranial hemorrhage between treatment arms(8). A recent, multicenter trial (PlaNeT-2) reported a higher risk of death or serious new bleeding among infants transfused at a higher (50,000/μL), compared to lower (25,000/μL), platelet threshold(9**). This trial also found a higher risk of bleeding with a more liberal approach to platelet transfusion using higher thresholds. Another recent trial evaluated the effect of a higher platelet transfusion threshold on time to closure of a patent ductus arteriosus and found no difference between liberal and restrictive threshold arms(10). However, there were more incident cases of IVH among those infants in the liberal, as compared to the restrictive, transfusion arm (41% vs. 9%, P=0.03).
These studies highlight concerns with the use of liberal thresholds for prophylactic platelet transfusion in neonates, which is supported by biologic plausibility of potential adverse effects from pro-inflammatory and vasoactive factors in platelets(11*). Implementation of a restrictive platelet transfusion guideline is associated with reduced platelet transfusion without increases in IVH(12). Therefore, recent data support the use of a restrictive transfusion threshold of 25,000/μL for prophylactic platelet transfusions in preterm neonates. However, there is uncertainty regarding the effect of lower thresholds among the most immature neonates during the highest-risk period of bleeding in the first week of life(13*).

**Term neonates**—Several sub-populations of term neonates are at high-risk of bleeding. Among neonates with hypoxic-ischemic encephalopathy, bleeding occurs in 28%, with 21% receiving platelet transfusion(14). One study suggested a platelet transfusion threshold of 130,000/μL to prevent bleeding in this population(15). However, in another study, initial thrombocytopenia (<100,000/μL) was uncommon among neonates with the most severe grades of bleeding, although initial thrombocytopenia was associated with any severity of bleeding(14). Neonates receiving ECMO are at high-risk of bleeding due to heparinization, along with thrombocytopenia and/or platelet dysfunction. Common thresholds range between 50,000–100,000/μL, although no trials have compared the efficacy and safety of higher vs. lower thresholds in this population (16, 17). Among neonates with neonatal alloimmune thrombocytopenia (NAIT), platelet thresholds of 50,000/μL are commonly used in the early postnatal period (e.g. first week of life) with more restrictive thresholds (∼30,000/μL) following this period. Initially, the use of platelets will transiently increase the platelet count (18–20), although transfusion of HPA-1a or 5b antigen negative platelets may be needed, and occasionally, the use of maternal platelets (21).

**Platelet Thresholds for Transfusion in Children**

Hypoproliferative thrombocytopenia, resulting from chemotherapy or radiation, is a common reason for platelet transfusion in children. These children are at a higher risk of bleeding than adults, which may be attributable to chemotherapy intensity as well as functional differences in interactions between the vascular endothelium and platelets(22). Myelodysplasia, marrow infiltrative processes, bone marrow failure syndromes, congenital platelet disorders, and aplastic anemia may also lead to decreased platelet production, necessitating platelet transfusion.

**Therapeutic Platelet Transfusion in Children with Bleeding**—Platelet transfusion should be considered in any pediatric patient with thrombocytopenia and active bleeding, with transfusion thresholds being situation dependent (Table 2). Patients with congenital platelet disorders, treatment-associated hypoproliferative thrombocytopenia, those undergoing hematopoietic stem cell transplantation (HSCT), on ECMO, or undergoing surgery may also benefit from platelet transfusion when bleeding.

**Prophylactic Platelet Transfusion in Children at Risk for Bleeding**—Much more controversy exists around thresholds for prophylactic platelet transfusions. A paucity of pediatric data exists in this area. Extrapolation from adult data occurs, with AABB...
guidelines recommending that adult patients with hypoproliferative thrombocytopenia be transfused at a platelet count ≤ 10,000/μL to prevent spontaneous bleeding(23). However, equipoise among pediatric hematology/oncology clinicians and pediatric intensivists exists regarding thresholds for children with hypoproliferative thrombocytopenia (24, 25). In 2016–2017, Nellis and colleagues executed an international study of platelet transfusions in critically ill pediatric oncology patients(26*). Two-hundred and thirty-seven children, 3 days to 16 years, were studied. Over 70% of platelet transfusions were given prophylactically and 59% were administered for a platelet transfusion threshold > 20,000/μL. No differences were discovered when comparing median platelet transfusion thresholds between bleeding and non-bleeding patients. Another single institution study revealed that the median platelet transfusion threshold for pediatric oncology patients with hypoproliferative thrombocytopenia was 16,000/μL(27). Additionally, a 2013 survey of Children’s Oncology Group Stem Cell Transplant Directors described that 69% of institutions transfused non-transplant oncology patients for platelet counts below 10,000/μL, with 27% of institutions transfusing these patients for platelet counts below 15,000/μL (25). This survey also found prophylactic transfusion thresholds for HSCT patients to be higher: 47% below 10,000/μL versus 44% below 20,000/μL(25).

However, the largest and most comprehensive transfusion study performed to date on patients with hypoproliferative thrombocytopenia was the Optimal Platelet Dose Strategy to Prevent Bleeding in Thrombocytopenia Patients or PLADO study. In a pediatric sub-analysis where the prophylactic transfusion threshold was ≤10,000/μL(28), data provided insight into bleeding and use of this evidenced-based lower platelet transfusion threshold in adults(29). PLADO enrolled 200 children (0–18 years of age)(22), and evaluated the relationship between platelet dose and bleeding. Participants were randomized to a low (1.1 × 10^{11}/m^2), medium (2.2 × 10^{11}/m^2), or high (4.4 × 10^{11} /m^2) platelet dose when the prophylactic platelet transfusion threshold was met. Platelet dose did not predict bleeding, however children overall had a significantly higher incidence of World Health Organization grade 2 or higher bleeding compared to adults (86% of children 0–5 years of age, 88% of children 6–12 years of age, 77% of children 13–18 years of age, compared to 67% of adults) and more days of bleeding (median of 3 days compared to 1 day in adults). Bleeding was most prominent in children undergoing HSCT. Further, pediatric patients were at a higher risk of bleeding over a wider range of platelet counts. When integrating these results together, factors beyond platelet counts alone may impact bleeding risk in children, demonstrating the need for additional studies(22).

Another area where evidence is scant and there is extrapolation from adult guidelines is transfusion for platelet counts < 20,000/μL prior to central line placement and for platelet counts < 50,000/μL prior to non-CNS surgeries(23). Additionally, there is debate surrounding guidelines for lumbar puncture (LP) in children. The 2014 AABB guidelines for adults recommended transfusing for platelet counts < 50,000/μL prior to lumbar puncture. For children if there are circulating blasts, case reports suggest 100,000/μL as a threshold, especially if there is a traumatic lumbar puncture, as a means of improving event-free survival of these patients(30–34). Thus, transfusing children with new onset leukemia to platelet counts above 100,000/μL prior to their initial LP may be considered, though national pediatric guidelines suggest 50,000/μL(35).
A recent multi-center, prospective, point prevalence study further demonstrated the variability in platelet transfusion thresholds, not only in children with cancer but also in critically ill children. In this study, 67% of children received prophylactic platelet transfusions, and 34% were administered for platelet counts greater than 50,000/μL (36*), with little data to support these practices.

**Use of ABO-mismatched Platelet Transfusions**

Platelets selected for transfusion to neonates and children in the US may either be apheresis- or whole blood-derived donor products. ABO-compatible platelets or identical platelets are ideally selected for transfusion to minimize the passive transfer of incompatible plasma containing isohemagglutinins, anti-A, anti-B, or anti-A,B antibodies (platelets from an O donors to A, B, or AB recipients, or from A or B donors to AB recipients, or from A or B donors to AB recipients) that may cause hemolysis in the recipient resulting in morbidity and mortality (37, 38) and to minimize the destruction of platelets expressing incompatible ABO antigens (39). Specifically, there have been 3 case reports of children dying from ABO-incompatible platelet transfusion, an 8 month old, 15 year old, and a 16 year old (40–42). In all 3 cases the patient ABO type was A and the platelet product was from an apheresis O donor. The anti-A titers ranged from 1:128 to 1:8000. There have been at least 7 reports of morbidity in children receiving ABO-incompatible platelet transfusions, with ages ranging from 9 days to 18 years of age, and anti-A titers ranging from < 1:20 to 1:32,000 (37). The plasma volume of children is small, and unable to dilute and accommodate the higher out-of-group ABO titers in addition to the large volumes of plasma that are transfused during platelet transfusions, and is the likely underlying context for much of the morbidity and mortality reported with ABO-mismatched platelet transfusions in neonates and children.

Other clinical benefits associated with ABO matching of platelets for transfusion include improved platelet recovery in vivo (39, 43–47), reduction in transfusion reactions and RBC alloimmunization (48), reduction in ABO immune complex formation (49), and improved post-transfusion platelet survival. Many of these effects may be seen with repeated platelet transfusion, not just upon a single transfusion. For instance, in a study of oncology patients, there was no difference in post-transfusion platelet count increment between use of ABO-mismatched versus ABO matched platelet transfusions, although a platelet refractory state was increased with multiple transfusions of ABO-mismatched platelets (50). These findings somewhat contrast with a recently published large PICU study in which no differences were seen in the incremental change in platelet count or in transfusion reactions when comparing a single transfusion of ABO mis-matched to ABO-matched platelet transfusions in critically ill children (51**).

Despite the goal in pediatrics to administer ABO-compatible or identical platelets, the lack of available products with these specifications occurs and challenges exist daily due to the short storage time of platelets of 5–7 days, resulting in out-dating of supplies and ultimately hindering the ability to consistently meet the demands of patients (48). Hence, other less desirable strategies are employed to mitigate hemolytic consequences, such as washing or volume reducing ABO-mismatched platelets. These procedures cause delays in issuing and decrease the efficacy and potency of the products, but still maintain functional platelets for...
transfusion\(^{(52)}\). Platelet additive solutions, another potential hemolysis risk-mitigation strategy when ABO mis-matched platelets are given, was recently shown to decrease plasma isohemaglutinin titers and transfusion reactions\(^{(53)}\). This strategy, although promising, must be studied in neonates and children prior to application.

**Use of Pathogen Reduced Platelets**

Although transfusion-transmitted infection is uncommon, concerns remain regarding emerging pathogens, such as Zika virus, as well as bacterial contamination of platelet products; the latter may account for 10\% of transfusion-related deaths\(^{(54,55)}\). This is highlighted by a report of four patients with sepsis following transfusion of apheresis platelets contaminated with bacteria\(^{(56**)\). Given these concerns, pathogen reduction technologies offer the potential to eliminate or inactivate viral, bacterial and parasitic pathogens in platelets. One system (INTERCEPT, Cerus Corporation, California) is currently FDA-approved for use in pediatric patients in the US and another system (MIRASOL, Terumo BCT, Colorado) is approved for use in Europe and is currently undergoing trials in the US. These systems use a photoactive compound (e.g. amotosalen in INTERCEPT or riboflavin in MIRASOL) that, when exposed to ultraviolet light, prevents the DNA replication necessary for pathogen survival. However, neonatal and pediatric patients have been underrepresented in studies of these systems and data suggest that pathogen reduced platelets may increase the risk of platelet refractoriness and increase platelet transfusion requirements in some populations\(^{(57)}\). In addition, there is the potential for skin rashes among neonates who are receiving pathogen reduced platelets containing psoralen compounds, such as amotosalen, while also receiving concomitant phototherapy using devices with a peak wavelength of 425 nm (interceptbloodsystem.com). In a recent 21-month single-center report, the use of pathogen-reduced platelets was associated with increased platelet utilization in the pediatric population, but similar rates of adverse events were noted between neonates and pediatric patients transfused with conventional vs. pathogen-reduced platelets\(^{(58**)\). As some blood banks adopt a larger or exclusive inventory of pathogen-reduced platelets, studies examining potential effects on platelet refractoriness and the potential adverse effects on clinical outcomes, such as bleeding and mortality, should be encouraged in the neonatal and pediatric population. Also, as noted in a recent report, bacterial contamination may still occur with the use of pathogen-reduced platelets\(^{(56**)\).}

**Conclusion**

Our review highlights recent advances in neonatal and pediatric platelet transfusion and also emphasizes the urgent need for better evidence to guide practice given recent studies showing the potential harms of platelet transfusion, particularly with liberal use, in preterm neonates.

**Acknowledgments**

Financial support and sponsorship:

This work was supported by the National Institutes of Health under award K23 HL128942 (R.M.P.).
References

Papers of particular interest, published within the annual period of review in the past 18 months have been highlighted as:

* of special interest

** of outstanding interest


26. Nellis ME, Goel R, Karam O, Cushing MM, Davis PJ, Steiner ME, et al. International Study of the Epidemiology of Platelet Transfusions in Critically Ill Children With an Underlying Oncologic Diagnosis. Pediatr Crit Care Med. 2019. This large analysis of critically ill oncology patients from around the world demonstrated that a majority of patients are transfused platelets for thresholds of 30,000–50,000/μl in both bleeding and non-bleeding circumstances and that prophylactic platelet transfusion are administered for higher thresholds than what guidelines recommend.


Key points:

- Recent trials support using restrictive platelet transfusion thresholds of 25,000/μL for prophylactic transfusions in preterm neonates, although the effect on bleeding among the most immature infants during the highest risk period of bleeding in the first week of life is uncertain.

- Debate and variable practices for prophylactic platelet transfusions continue in children due to the lack of studies including those patients with hypoproliferative thrombocytopenia.

- ABO mis-matched platelet transfusions have resulted in morbidity and mortality in infants and children, although the shortage of platelet products (due to short storage time and limited platelet donors) challenges the ability to consistently administer ABO-identical or compatible products.

- Hemolytic risk mitigation strategies, such as volume reduction, washing, and the use of platelet additive solutions, may provide safer ABO-mismatched platelet products to infants and children.

- Pathogen-reduced platelets may decrease the risk of transfusion-transmitted infection, but may also increase the risks of platelet refractoriness and transfusion requirements based on data largely derived from transfused adults; thus, additional studies are necessary to elucidate the effects of pathogen-reduced platelet transfusions in the neonatal and pediatric population.
Table 1.
Trials Comparing Platelet Transfusion Approaches in Preterm Neonates

<table>
<thead>
<tr>
<th>Trial:</th>
<th>Andrew et al.(8)</th>
<th>Curley et al.(9**)</th>
<th>Kumar et al.(10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>GA &lt; 33 weeks, birthweight 500–1500 g, and platelets &lt; 150 × 10^9/L (N=152)</td>
<td>GA &lt; 34 weeks’ and platelets &lt; 50 × 10^9/L (N=660)</td>
<td>GA &lt; 35 weeks’, hemodynamically significant PDA and platelets &lt; 100 × 10^9/L (N=44)</td>
</tr>
<tr>
<td><strong>Intervention/Comparison</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher platelet transfusion threshold</td>
<td>150,000/μL</td>
<td>50,000/μL</td>
<td>100,000/μL</td>
</tr>
<tr>
<td>Lower platelet transfusion threshold</td>
<td>50,000/μL or bleeding</td>
<td>25,000/μL</td>
<td>20,000/μL*</td>
</tr>
<tr>
<td><strong>Outcome (primary)</strong></td>
<td>New intracranial hemorrhage</td>
<td>Death or new major/ severe bleeding</td>
<td>Time to PDA closure</td>
</tr>
<tr>
<td><strong>Time to follow-up for primary outcome</strong></td>
<td>7–10 days</td>
<td>28 days after randomization</td>
<td>120 hours after randomization</td>
</tr>
<tr>
<td><strong>Summary of results for primary outcome</strong></td>
<td>No difference 28% vs. 26%, P=0.73</td>
<td>Worse with higher platelet transfusion threshold OR 1.57 (95% CI 1.06–2.32), P=0.02</td>
<td>No difference Adjusted HR 1.4 (95% CI 0.57–3.47), P=0.46</td>
</tr>
</tbody>
</table>

Abbreviations: GA, gestational age; PDA, patent ductus arteriosus; OR, odds ratio; HR, hazard ratio

*without surgery or bleeding
Table 2.

Platelet Transfusion Thresholds in Children

<table>
<thead>
<tr>
<th>Indication</th>
<th>Platelet transfusion threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>Dependent on degree and underlying reason for bleeding</td>
</tr>
<tr>
<td>Bleeding on ECMO or during surgery</td>
<td>50,000–100,000/μL</td>
</tr>
<tr>
<td>Prophylaxis for hypoproliferative thrombocytopenia</td>
<td>10,000/μL (15,000–20,000/μL for HSCT)</td>
</tr>
<tr>
<td>Prophylaxis for line placement</td>
<td>20,000/μL</td>
</tr>
<tr>
<td>Prophylaxis for lumbar puncture</td>
<td>50,000–100,000/μL (higher threshold considered when circulating blasts present)</td>
</tr>
<tr>
<td>Prophylaxis for CNS bleeding in children with sickle cell disease</td>
<td>30,000–50,000/μL</td>
</tr>
<tr>
<td>Prophylaxis for major surgery</td>
<td>50,000/μL (prophylaxis may be higher for CNS surgery)</td>
</tr>
<tr>
<td>Platelet dysfunction with bleeding and/or in need of an invasive procedure</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Abbreviations: ECMO, extracorporeal membrane oxygenation; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation.