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Platelet Transfusions in the NICU

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Introduction

Thrombocytopenia, generally defined as a platelet count less than $150 \times 10^9/L$, is (after anemia) the second most common hematologic disorder of infants admitted to neonatal intensive care units (NICUs). It affects 18–35% of all patients admitted to NICUs and approximately 70% of extremely low birth weight (ELBW) infants with a birth weight less than 1,000 grams.^{1–4} The incidence of thrombocytopenia is inversely proportional to the gestational age, and it represents a risk factor for poor neonatal outcomes.⁵

Recently, Wiedmeier and collaborators published the largest study on neonatal platelet counts conducted to date, which included approximately 47,000 infants delivered between 22 and 42 weeks gestation.⁶ This study showed that platelet counts at birth increased with advancing gestational age (Figure 1). Linear regression analysis showed that, for each week increase in gestational age, there was a corresponding increase in mean platelet count of approximately $2 \times 10^9/L$. Importantly, while the mean platelet count was $200 \times 10^9/L$ even in the most preterm infants, the 5th percentile in this large epidemiological study was $104 \times 10^9/L$ for those ≤ 32 weeks gestation and $123 \times 10^9/L$ for late-preterm and term neonates (Figure 1A).⁶ These findings indicated that different definitions of thrombocytopenia should be applied to preterm infants.

The etiologies of thrombocytopenia are highly diverse, as is the natural history. Clinically, a distinction is frequently made between “early onset” (≤ 3 days of life) and “late onset” (> 4 days of life) neonatal thrombocytopenia. Intra-uterine growth restriction, pregnancy induced hypertension or diabetes, perinatal infection, and transplacental passage of maternal allo- or autoantibodies are frequently associated with early onset thrombocytopenia. Late onset

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neonatal thrombocytopenia is most commonly due to bacterial infection or necrotizing enterocolitis.

Platelet transfusion practices

Platelet transfusion remains the primary treatment modality for neonatal thrombocytopenia, but there is lack of agreement regarding the platelet count below which a newborn infant should be transfused. Nevertheless, it has been widely accepted that neonates should be transfused at higher platelet counts than older children and adults, and thus platelet transfusions are a frequent intervention in the NICU. In an earlier study of a single NICU in the U.S. with liberal transfusion practices, 9% of infants admitted received at least one platelet transfusion during their NICU stay.⁷ Extrapolating data from a single institution to the number of North-American NICU admissions over a one-year period, it was calculated that 80,000 platelet transfusions are administered annually to neonates in the U.S. (John Widness, U. of Iowa, personal communication). A recent survey of platelet transfusion practices among U.S. and Canadian neonatologists revealed wide practice differences in regard to platelet transfusion thresholds in different clinical scenarios, and suggested that a high proportion of platelet transfusions were given to non-bleeding neonates with platelet counts between 50 and $100 \times 10^9/L$, particularly in the first week of life.⁸

In order to compare transfusion practices in North America with those in Europe, the same survey was translated to German and sent to all NICU directors in German-speaking European countries (Germany, Austria, and Switzerland). The transfusion thresholds chosen by North American and European neonatologists in each clinical scenario were then compared. In this study, European neonatologists selected substantially lower platelet transfusion thresholds than North-American neonatologists in nearly all case scenarios (Figure 2), with the exception of neonatal alloimmune thrombocytopenia and prior to invasive procedures. It was estimated from survey responses that practice differences alone would account for 1.8 times more platelet transfusions given in U.S. compared to European NICUs.⁹ In a subsequent prospective multicenter observational study performed in the UK, thrombocytopenic neonates were transfused at a median platelet count of $27 \times 10^9/L$, confirming the use of more restrictive transfusion thresholds in European countries.¹⁰ A single retrospective study of platelet transfusions in a Mexican NICU suggested that practices in that country resembled the European restrictive approach.¹¹

The reasons underlying this practice variability are probably multifactorial, but most likely involve the lack of solid evidence from randomized controlled trials to guide neonatal transfusion decisions, the high incidence of bleeding in this population, and the known platelet hyporeactivity of neonates.

Primary Hemostasis in the Neonate

Multiple studies evaluating platelet activation and aggregation clearly demonstrated that neonatal platelets are hyporesponsive *in vitro* to most agonists (including ADP, epinephrine, collagen, thrombin, and thromboxane analogs), compared with adult platelets.^{12,13} The underlying mechanisms responsible for the decreased platelet responses are different for each agonist. Specifically, the lack of response to epinephrine is explained by the presence

of fewer α_2 -adrenergic receptors on neonatal platelets,¹⁴ the diminished response to collagen is likely a consequence of impaired calcium mobilization,¹⁵ and the reduced response to thromboxane is due to differences in signaling downstream from the receptor in neonatal platelets.¹² Recently, decreased expression of PAR-1 and PAR-4 receptors was described in neonatal platelets, thus explaining the decreased response to thrombin.^{16,17} While this platelet hyporeactivity would have been expected to result in a bleeding tendency, Andrew *et al.* in 1999 reported that full term neonates had *shorter* bleeding times (BTs) than healthy adults.¹⁸ Subsequent studies using the Platelet Function Analyzer (PFA-100®), \test of primary hemostasis, also showed that PFA-100 closure times (CTs) were shorter in full term infants compared to healthy adults. Taken together, these studies demonstrated that full term neonates have adequate primary hemostasis, despite their *in vitro* platelet hyporeactivity.^{19,20} This seemingly paradoxical finding is due to the presence of compensatory factors in neonatal blood that enhance clot formation and perfectly balance the hyporeactivity of neonatal platelets, leading to normal BTs and CTs. These compensatory factors include the high hematocrits in neonatal blood, the high MCV of neonatal red cells, and the predominance of ultralong polymers of von Willebrand Factor, which is also present at high concentrations in neonatal plasma. Thus, *the hyporeactivity of neonatal platelets should not be considered a developmental deficiency or a factor that confers a bleeding tendency, but rather part of a carefully balanced and unique hemostatic system.*

Most studies evaluating bleeding and closure times were conducted in cord blood from full term infants, and there is limited data in preterm neonates. However, the existing studies suggest that the platelet hyporeactivity is somewhat more pronounced^{21,22} and might be less well compensated in preterm neonates, which in turn might translate into a more vulnerable hemostatic system. Specifically, BTs performed on the first day of life were longer in preterm compared with term infants, with neonates <33 weeks gestation exhibiting the longest bleeding times (approximately double those from adults).²³ Saxonhouse *et al.* found that PFA-100 CTs from non-thrombocytopenic neonates were inversely correlated to gestational age in both cord blood and neonatal peripheral blood samples obtained on the first day of life.²⁴ Importantly, however, while these BTs and CTs were longer in preterm compared to term neonates, they were still near or within the normal range for adults, suggesting that healthy preterm neonates also have adequate primary hemostasis. Data regarding how disease processes perturb this delicate system, particularly in the preterm neonate, are lacking.

In vitro studies using flow-cytometry or the cone and platelet analyzer showed that the neonatal platelet function improves significantly and nearly normalizes by 10–14 days, even in preterm infants.^{21,22,25} Consistent with this, Del Vecchio *et al.* found that, by day of life 10, all infants had shorter BTs than at birth, and early gestational age-related differences had disappeared. Moreover, little or no further shortening occurred between days 10 and 30.²³ While no causal association has been demonstrated, these findings correlate well with the clinical observation that the highest risk of bleeding among NICU patients is found in preterm neonates during the first 10 days of life.¹⁰

Relationship between severity of thrombocytopenia and bleeding risk

The combination of thrombocytopenia and platelet dysfunction in neonates has been invoked as a potential contributor to the high incidence of intraventricular hemorrhage (IVH) in preterm infants. In that regard, several studies have shown an association between thrombocytopenia and IVH, although this does not establish causality. Importantly, the majority of neonates who experience IVH have normal or minimally decreased platelet counts at the time of their bleeds, highlighting the fact that the pathogenesis of IVH in this patient population is complex and multifactorial, likely primarily involving cardiovascular instability and vascular fragility.

The relationship between degree of thrombocytopenia and bleeding risk has been assessed in a number of neonatal studies. The first large prospective observational study to evaluate this was published by Andrew et al. in 1992. This study used a hemorrhagic score to evaluate bleeding in neonates, and found that thrombocytopenic infants were two and a half times more likely to bleed than non-thrombocytopenic infants. Among VLBW infants (<1500 gram), thrombocytopenia was associated with a higher incidence of grade III or IV IVH (44% vs. 16% in non-thrombocytopenic neonates).¹ Although there was a moderate inverse correlation between platelet count and hemorrhagic scores, this was confounded by the fact that the infants with the lowest platelet counts were more likely to have DIC than the non-thrombocytopenic neonates.¹

A contemporary prospective multicenter observational study by Stanworth *et al.* (PlaNeT-1 study) found that approximately 25% of thrombocytopenic neonates had platelet counts $<60 \times 10^9/L$, and 9% of them experienced clinically significant bleeding (most commonly intracranial).¹⁰ 87% of these hemorrhages occurred during the first two weeks of life and 87% were in neonates <28 weeks gestation. However, nadir platelet counts were similar in infants who had either no bleeding, only minor bleeding, or severe bleeding (Figure 3). Furthermore, a secondary analysis found that a lower nadir platelet count was associated with only a slightly increased number of bleeding events. The strongest predictors of hemorrhage were gestational age <28 weeks, postnatal age <10 days, and diagnosis of NEC.²⁶

Two other recent retrospective studies have assessed bleeding in neonates with thrombocytopenia. One of them reported an association between severity of thrombocytopenia and cutaneous and gastrointestinal bleeding. However, neither study found a correlation between severity of thrombocytopenia and other types of major bleeding, including IVH.^{27,28}

Taken together, the evidence indicates that, while thrombocytopenia is a risk factor for bleeding in neonates, there is a poor correlation between severity of thrombocytopenia and clinically significant bleeding. This suggests that thrombocytopenia might be a marker of severity of illness, and that factors other than the platelet count determine the bleeding risk. The latter is supported by the finding that gestational age <28 weeks, postnatal age <10 days, and diagnosis are NEC are far stronger predictive factors of bleeding among thrombocytopenic neonates than the platelet count itself. The lack of inverse correlation

between platelet counts and bleeding risk has also been reported in recent studies of children with thrombocytopenia secondary to chemotherapy or myeloablation.²⁹

Do platelet transfusions decrease the incidence of bleeding?

Platelet transfusions constitute the only readily available specific treatment for thrombocytopenia in neonates. Although platelet transfusions are frequently given to neonates with platelet counts below a certain arbitrary trigger, there is no good evidence to determine which neonate would benefit from a transfusion. In contrast to the multiple platelet transfusion trigger studies that have been performed in thrombocytopenic adults, the only platelet transfusion trigger trial performed in preterm infants was underpowered and was conducted >20 years ago.³⁰

This landmark trial assessed the effects of prophylactic platelet transfusions in 152 VLBW infants with mild-to-moderate thrombocytopenia (platelet counts $50\text{--}150 \times 10^9/\text{L}$) in the first week of life, and found that the incidence of IVH was not different when the platelet count was maintained $>150 \times 10^9/\text{L}$ vs. allowed to fall to $60 \times 10^9/\text{L}$ prior to transfusion (28 vs. 26%, respectively).³⁰ Unfortunately, patients with severe thrombocytopenia ($<50 \times 10^9/\text{L}$) and infants older than 7 days were excluded from the study. Thus, while this trial clearly indicated that transfusing VLBW infants with platelet counts $>60 \times 10^9/\text{L}$ in the first week of life does not reduce the incidence or severity of IVH, it remained unclear whether lower platelet counts could be safely tolerated in this population.

In the prospective observational PlaNeT-1 study, conducted in the United Kingdom, platelet transfusions were administered at a median platelet count of $27 \times 10^9/\text{L}$. In a secondary analysis, the temporal association between platelet transfusions and minor bleeding was assessed. This analysis showed that neonates had 21% fewer bleeding events during the 12 hours following a platelet transfusion compared with the 12 hours prior to transfusion.²⁶ However, these findings should be interpreted with caution, partly because of the study design (observational study being prone to confounders and lacking control group), and because these results were part of a secondary analyses. More recently, von Lindern *et al.* compared the bleeding outcomes in NICUs that used liberal transfusion thresholds with NICUs that used restrictive indications for platelet transfusions. These investigators found no significant differences between units.

While there is limited evidence for the efficacy of platelet transfusions in neonates, several studies have reported a strong correlation between number of platelet transfusions and increased neonatal morbidity and mortality,^{7,11,31,32} and at least one has suggested that this increased mortality can be partially attributed to the platelet transfusions *per se*.³³ In the specific case of necrotizing enterocolitis, a common cause of thrombocytopenia, patients who developed short bowel syndrome or cholestasis received more platelet transfusions than those who did not (9 vs. 1.5 platelet transfusions, $p=0.01$).³² It remains unclear, however, whether this association simply reflects the fact that sicker infants receive more transfusions, or whether platelets contribute to the disease process in NEC. In that regard, it has become increasingly clear that platelets are active participants in immune and inflammatory processes.³⁴ It is also noteworthy that a multi-institutional analysis of complications from

blood transfusions in children demonstrated that platelet transfusions were associated with the highest incidence of complications among all blood components.³⁵ Data collected over 10 years from the UK Serious Hazards of Transfusion national hemovigilance scheme also indicated that neonates experience a disproportionately high number of overall transfusion adverse events, compared to pediatric and adult patients.³⁶ Among all of the potential risks associated with platelet transfusions, transfusion related acute lung injury (TRALI) deserves special consideration because (given the frequency with which neonates experience respiratory deterioration in the NICU), it is likely to be under-recognized and under-reported in this population.

Current recommendations

At this point, it is clear that additional well designed randomized controlled trials are needed to help identify safe and effective platelet transfusion thresholds for neonates. The PlaNeT-2 study is a large multicenter study conducted in several European countries that is comparing liberal vs. restrictive prophylactic platelet transfusion strategies in thrombocytopenic preterm infants (50 vs. $25 \times 10^9/L$, respectively).³⁷ Approximately 350 infants have been enrolled to date, of a planned total of 600 (Stanworth, Personal Communication).

While awaiting for results from PlaNeT-2, a number of guidelines have been published, which in general adhere to somewhat restrictive practices. In the UK, current advice is based on expert opinion. The recommendation is that prophylactic platelet transfusion be given to all neonates (term or preterm) with a platelet count $<20 \times 10^9/L$, to stable preterm infants if the platelet count falls below $30 \times 10^9/L$, and to all infants with a birth weight $<1,000$ g if the platelets are below $50 \times 10^9/L$ during the first week of life. Of note, a threshold of $50 \times 10^9/L$ is commonly used in the UK for infants who are clinically unstable, have had a previous major bleed, or have other known risk factors (i.e. NEC).³⁸ Christensen and collaborators recently published a compilation of evidence-based advances in transfusion practices in U.S. NICUs, and graded the quality of the evidence and the strength of their recommendations. Based on the guidelines from Intermountain Healthcare in Utah, U.S.A., these investigators recommended that stable NICU patients receive a platelet transfusion if the platelet count falls below $20 \times 10^9/L$, and unstable patients receive a transfusion for platelet counts $<50 \times 10^9/L$. However, the strengths of these recommendations were low and moderate, respectively, due to the lack of solid data to guide them.³⁹

The same group pioneered the application of platelet mass, which is the result of platelet count (per mL) X mean platelet volume. In a study conducted in two Intermountain Healthcare NICUs, platelet count-based guidelines were used for one year, and then switched to platelet mass-guided transfusion guidelines. Fewer transfusions were administered to neonates during the period of time using platelet mass-guided transfusions, and no differences were found in bleeding outcomes.⁴⁰ This approach has never been tested in a prospective randomized trial, however, and thus the strength of the recommendation was moderate/small. A pilot randomized trial conducted in 30 infants concluded that such a study would be feasible, although it would likely require a very large sample size.⁴¹

Acknowledging the paucity of solid evidence to guide transfusion decisions, and while awaiting the results of the PlaNeT 2 trial,³⁷ we currently recommend transfusing neonates according to the levels shown in Table 1.

Future Directions

While currently platelet transfusions are administered on the basis of platelet counts or platelet mass, the evidence strongly suggests that factors other than the degree of thrombocytopenia determine the bleeding risk. Thus, larger studies are needed to better characterize the platelet function and the hemostatic profile of preterm infants, and their changes over time and in response to illness. Along these lines, it will also be important to develop and validate tests that can be used in preterm infants and that incorporate both platelet count and function to evaluate hemostasis, rather than individual platelet factors alone.

The PFA-100 is an *in vitro* test of primary hemostasis that provides a quantitative measurement of platelet adhesion, activation, and aggregation in whole blood.⁴² As PFA-100 CTs represent global measurements of primary hemostasis, they are particularly attractive in neonates, since many factors contribute to their finely balanced hemostatic system. A recent pilot study by Deschmann et al., measuring PFA-100 CTs in thrombocytopenic neonates of various gestational and postnatal ages, showed that CT-ADP was a better marker for evaluating neonatal platelet function than CT-Epi, and identified a threshold effect of platelet counts on CT-ADP: all infants with platelet counts $>90 \times 10^9/L$ had normal CTs-ADP, and most infants with platelet counts $<90 \times 10^9/L$ had normal or minimally prolonged CTs-ADP, but a few exhibited significant prolongations.⁴³ A prospective observational study to evaluate whether a prolonged CT-ADP is a better marker of bleeding risk than the platelet count alone is currently in progress (Neo-HAT).

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Best Practices

What is the current practice?

1. Platelet transfusions are given to thrombocytopenic neonates at extremely variable platelet count thresholds, depending on gestational age, postnatal age, clinical condition, and individual preferences.
2. Surveys and observational studies suggest that platelet transfusion practices are significantly more liberal in North American compared to European NICUs.
3. Most platelet transfusions are given prophylactically to non-bleeding neonates with a platelet count below a certain threshold, based on minimal evidence. The only randomized controlled trial in the field demonstrated that very low birth weight infants in the first week of life who were transfused for any platelet count $<150 \times 10^9/L$ had the same incidence and severity of IVH than infants transfused for platelet counts $<50 \times 10^9/L$.
4. A prospective observational study of neonates with platelet counts $<60 \times 10^9/L$ showed that severity of thrombocytopenia was not a good predictor of bleeding. Gestational age <28 wks, age <10 days, and diagnosis of necrotizing enterocolitis were far stronger predictors of bleeding than the platelet count.

What changes in current practice are likely to improve outcomes?

1. Surveys suggest that sick neonates in North American NICUs are frequently transfused for platelet counts between 50 and $100 \times 10^9/L$, despite data from a randomized controlled trial indicating no benefit for transfusions at these counts.
2. Additional controlled randomized trials are needed to identify safe platelet transfusion thresholds in neonates of different gestational and post-natal ages. One such trial is currently comparing the safety and efficacy of using 50 vs. $25 \times 10^9/L$ as neonatal platelet transfusion thresholds (PlaNeT-2 trial).
3. Several studies have shown a poor correlation between platelet counts and bleeding risk, suggesting that other factors are more important determinants of bleeding. Thus, additional studies are needed to understand platelet function in preterm neonates, and to develop tests that better assess primary hemostasis and identify neonates at risk of bleeding.

Summary Statement

There is significant world-wide variability in platelet transfusion thresholds used to transfuse thrombocytopenic neonates. A large multicenter randomized controlled trial comparing two different platelet transfusion thresholds in neonates is currently ongoing, and should provide data to guide transfusion practice. However, several studies have found that factors other than the degree of thrombocytopenia determine the bleeding risk. Thus, it will be important to develop better tests to assess primary hemostasis and bleeding risk in neonates.

Key Points

- While currently platelet transfusions are administered on the basis of platelet counts or platelet mass, the evidence strongly suggests that factors other than the degree of thrombocytopenia determine the bleeding risk.
- Thus, larger studies are needed to better characterize the platelet function and the hemostatic profile of preterm infants, and their changes over time and in response to illness.
- It will be important to develop and validate tests that can be used in preterm infants and that incorporate both platelet count and function to evaluate hemostasis, rather than individual platelet factors alone.
- Intra-uterine growth restriction, pregnancy induced hypertension or diabetes, perinatal infection, and transplacental passage of maternal allo- or autoantibodies are frequently associated with early onset thrombocytopenia.

Figure 1.

First recorded platelet counts, obtained in the first three days after birth, in neonates born at 22 to 42 weeks gestation. Mean values are indicated by the red line, and the 5th and 95th percentiles are shown in the blue and green lines, respectively. *From: Wiedmeier SE et al., Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system. Journal of Perinatology 29:132, 2009; with permission.*

Figure 2.

Platelet transfusion thresholds selected by neonatologists in German-speaking European countries (AUT/GER/SUI, white bars) vs. U.S. neonatologists (black bars) in two different clinical scenarios. Neonatologists were asked when they would transfuse a two-day old stable preterm infant (left panel), or the same infant with bacterial sepsis (right panel).

From: Cremer M et al., Platelet transfusions in neonates: practices in the United States vary significantly from those in Austria, Germany, and Switzerland. *Transfusion* 51:2636-7, 2011; with permission.

Figure 3.

Lowest platelet counts in neonates with and without major or minor hemorrhage. Hatched lines indicate group medians; dashed lines represent IQRs. The lowest counts before hemorrhage are shown for neonates with minor or major hemorrhage, and the lowest counts during the thrombocytopenic episode are presented for neonates with no bleeding. *From: Stanworth SJ et al., Prospective, observational study of outcomes in neonates with severe thrombocytopenia. Pediatrics 124:e826, 2009; with permission.*

Table 1

Recommended transfusing levels for neonates

Platelet Count ($\times 10^9/L$)	Guidelines
<30	<i>Transfuse all</i>
30 – 49	<i>Transfuse if:</i> <ul style="list-style-type: none"> • BW <1,500 g and 7 days old • Clinically unstable • Concurrent coagulopathy • Previous significant hemorrhage (i.e. grade 3 or 4 IVH) • Prior to surgical procedure • Post-operative period (72 hours)
50 – 100	<i>Transfuse if:</i> <ul style="list-style-type: none"> • Active bleeding • NAIT with intracranial bleed • Before or after neurosurgical procedures

BW: Birth weight

NAIT: Neonatal Alloimmune Thrombocytopenia