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Review

# Thrombocytopenia and platelet transfusion in the neonate

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SUMMARY

Neonatal thrombocytopenia is widespread in preterm and term neonates admitted to neonatal intensive care units, with up to one-third of infants demonstrating platelet counts <150 × $10^9$/L. Thrombocytopenia may arise from maternal, placental or fetal/neonatal origins featuring decreased platelet production, increased consumption, or both mechanisms. Over the past years, innovations in managing neonatal thrombocytopenia were achieved from prospectively obtained clinical data on thrombocytopenia and bleeding events, animal studies on platelet life span and production rate and clinical use of fully automated measurement of reticulated platelets (immature platelet fraction). This review summarizes the pathophysiology of neonatal thrombocytopenia, current management including platelet transfusion thresholds and recent developments in megakaryopoietic agents. Furthermore, we propose a novel index score for bleeding risk in thrombocytopenic neonates to facilitate clinician's decision-making when to transfuse platelets.



## 1. Introduction

Thrombocytopenia, defined by a platelet count of <150 × $10^9$/L, is the most frequent hematologic disorder in neonates admitted to intensive care units (NICUs) with an incidence between 18% and 35% [1,2]. Usually, thrombocytopenia is classified as mild (platelet count 100–149 × $10^9$/L), moderate (platelet count 50–99 × $10^9$/L), and severe (platelet count <50 × $10^9$/L). The rationale behind such grading is weak, considering that plasma coagulation factors and other factors such as extreme prematurity significantly influence the individual bleeding risk [3–5]. In very low birth weight infants (VLBW; birth weight <1500 g), reference values for normal platelet counts are currently being debated: Van den Hof et al. determined platelet counts by cordocentesis in 229 fetuses. At 15 weeks of gestation post conceptional age, the mean platelet count was 187 ± 47 × $10^9$/L and increased to 274 ± 47 × $10^9$/L at 40 weeks of gestation [6]. Sainio et al. examined 4489 healthy term neonates in cord blood at delivery and measured a mean platelet count of 380 ± 69 × $10^9$/L [7]. The largest cohort examined by Wiedmeier et al. [8] included more than 47,000 neonates between 23 and 42 weeks of gestation with blood sampling in the first three days of life. The reference ranges for normal platelet counts were lower compared to previous published data generated in smaller cohorts. The lower range (5th percentile) for infants born ≤32 weeks of gestation was 104 × $10^9$/L, and 123 × $10^9$/L for late preterm and term neonates. Nevertheless, scientific data for actionable 'normal values' for hematological parameters is somewhat limited in preterm infants and healthy term neonates. Prematurity per se reflects an altered health status resulting from a diverse group of underlying maternal or fetal diseases, which might affect the platelet count; and healthy neonates generally undergo no blood sampling for ethical reasons. These facts may also explain the lower reference range described in preterm neonates and term neonates who underwent a collection of platelet counts due to a clinician's order, which is founded on a different clinical condition than in 'normal' patients. In particular, if the implication of a certain platelet number with regard to the underlying cause of severe or even mild thrombocytopenia is uncertain, there is a need for additional parameters in order to judge the megakaryopoietic activity and the individual bleeding risk. This is a focus of current efforts in clinical research.

## 2. Neonatal megakaryopoiesis and platelet function

### 2.1. Developmental characteristics of neonatal megakaryopoiesis

Fetal and neonatal megakaryopoiesis, platelet morphology and function underlying developmental changes need to be

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considered. During human embryogenesis, megakaryocyte progenitors and megakaryocytes can be detected in the yolk sac as early as five weeks post conceptional age. These cells switch to the liver in the second month of gestation [9], while transitioning to the bone marrow begins at four months of gestation, and is nearly completed at term. In the late fetal and neonatal period, megakaryocytes are structurally and functionally different from those found in adults, being smaller and having a lower ploidy (mostly 2N/4N) than adult cells (64N) [10,11]. Presumably, this leads to a smaller number of platelets generated per megakaryocyte. The limited release of platelets is compensated by a 10-fold higher megakaryocyte proliferation rate as compared to adult cells. Despite the lower ploidy, the cytoplasmatic maturation process is accelerated by high expression of the transcription factor GATA-1 [12]. Neonatal megakaryocyte progenitors are more sensitive to the actions of thrombopoietin [12] than adult cells responding in vitro to thrombopoietin concentrations as low as 1 ng/mL [13].

Thrombopoietin plasma concentrations are higher in non-thrombocytopenic neonates compared to adults and exhibit a characteristic course in the neonatal period. At birth the median thrombopoietin concentration is 124 pg/mL (range 48–225 pg/mL), increasing with a peak at day 2–5 (median 196 pg/mL, range 144–305 pg/mL), before decreasing to only slightly higher levels than in infants or older children by the end of the neonatal period (median 70 pg/mL, range 35–141 pg/mL) [14]. Several studies analyzing the relationship between plasma thrombopoietin levels and platelet counts in prematurity demonstrate that thrombopoietin concentrations rise during thrombocytopenia, but are rather low compared to those in term neonates and adults [15,16]. As indicated by experimental studies, neonatal platelets survive one day longer in the circulation, also contributing to the expansion of the neonatal platelet mass during the first two postnatal weeks [17]. All these physiological differences lead to a comparable production rate compared to adults.

### 2.2. Neonatal platelet function

Hemostasis in neonates is a delicate balance between pro- and anticoagulatory factors, in which platelets mediate primary hemostasis, avoiding the development of pathological thrombus formation while facilitating the response to hemorrhage. Notably, platelets of healthy term neonates are less responsive to platelet agonist, exhibit fewer $\alpha_2$-adrenegic receptors on their surface, reduced calcium mobilization, and differences in thromboxane receptor signaling. However, the bleeding time and the closure times in Platelet Function Analyzer-100 (PFA-100; Siemens, Erlangen, Germany) studies are shorter [18], likely because of higher hematocrit, higher mean corpuscular volume, higher von Willebrand factor (vWF) concentrations, and predominance of longer vWF multimers [19]. This indicates that platelet hyporeactivity in healthy full-term neonates is an integral part of a delicately balanced neonatal hemostatic system, rather than a developmental deficiency. In preterm infants, platelet hyporeactivity is even more pronounced than in full-term neonates due to lower platelet adhesion (although still higher than in healthy adults) [20,21]. Bleeding times and closure time correlate inversely with gestational age [22]. However, despite the pronounced platelet hyporeactivity, it is thought that preterm infants also have adequate primary hemostasis [23]. Currently, a prospective, observational study, the 'Neonatal Hemorrhagic Risk Assessment in Thrombocytopenia' study, is recruiting VLBW infants to evaluate whether the PFA-100 closure time is a better predictor of clinical bleeding than platelet counts alone [24].

## 3. Incidence and etiologies of thrombocytopenia

### 3.1. Incidence of thrombocytopenia

For methodological reasons, information on the incidence of neonatal thrombocytopenia should be considered carefully. Challenges in sampling blood from ill neonates, especially heel stick samples, can result in artificial lowering of counts due to clumping of platelets. Thus, a low platelet count should always be confirmed to exclude any pre-analytical errors. Furthermore, the methods for determining the platelet number differ both regarding the type of blood sample and the technical examination. Modern automated hematology analyzers measure the platelet count by the electric impedance method. In abnormal blood samples, such as those with large platelets or small red blood cells, a computer algorithm is applied that switches measurement to the optical method, which detects the scattered light of blood cells by flow cytometry [25].

The definition of normal ranges differs, particularly in very preterm infants and in specific types of thrombocytopenia, such as alloimmune thrombocytopenia [7]. At birth, the incidence of thrombocytopenia defined by a platelet count $<150 \times 10^9$/L is 0.12–0.24% of all neonates [7,26]. About 0.1–2% of all infants develop thrombocytopenia during the neonatal period (days 1–28) [7]. Importantly, 18–35% of all preterm and term neonates admitted to NICUs exhibit a platelet count $<150 \times 10^9$/L at least once [1,2]. In extremely low birth weight (ELBW; <1000 g) infants, the incidence of thrombocytopenia reaches up to 73% [5]. Among thrombocytopenic ELBW infants, almost 40% have severe thrombocytopenia ($<50 \times 10^9$/L). If the platelet counts fall to $<20 \times 10^9$/L the risk for bleeding increases [27], whereas the clinical significance of a platelet count between 100 and $150 \times 10^9$/L remains controversial.

### 3.2. Etiologies of thrombocytopenia

The principal pathophysiologic mechanisms of neonatal thrombocytopenia include:

- decreased production of platelets;
- increased intravascular consumption of platelets;
- extravascular loss of platelets due to bleeding, platelet fragmentation (e.g. extracorporal membrane oxygenation, surgery with cardiopulmonary bypass, or exchange transfusion).

Often, the exact assignment to one of these mechanisms is not possible. Thrombocytopenia, primarily caused by increased consumption, can be exacerbated by decreased or inadequately low platelet production. This, in particular, affects sick preterm infants, whose megakaryopoiesis can be exhausted after prolonged stimulation or with inadequate thrombopoietin synthesis due to impaired liver function.

When evaluating thrombocytopenia, three key points are fundamental to address:

1. Time of onset of thrombocytopenia, distinguishing 'early-onset' (within 72 h after birth) from 'late-onset' thrombocytopenia.
2. Primary origin (maternal, placental, or neonatal/fetal cause).
3. Individual bleeding risk.

The diagnostic approach should begin with clinical examination for bleeding signs. Minor bleeding can be defined as blood staining of oral, nasogastric, or endotracheal secretions or stool, as well as hematuria, petechiae, or oozing from puncture sites [28]. Major bleeding includes pulmonary or intracerebral bleeding. The physical examination focuses on the general condition and any signs of congenital infection, hepatosplenomegaly, jaundice, stigmata