Thrombocytopenia in the Newborn

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Education Gaps

1. Knowing the differential diagnosis and most likely etiologies of thrombocytopenia in the neonate will lead to more appropriate diagnostic evaluations and treatments.

2. Thrombocytopenia may be a symptom of various congenital or acquired conditions in the neonatal period and should prompt further diagnostic evaluations.

Abstract

Neonates develop thrombocytopenia from a multitude of causes, including immune-mediated conditions, infections, inherited disorders, and acquired conditions such as thrombosis. This can make it challenging to diagnose an underlying cause and the evaluation can be extensive. This article will provide strategies to facilitate the evaluation of thrombocytopenia in the newborn and provide a background for the underlying pathophysiology of this condition and its various causes.

Objectives

After completing this article, readers should be able to:

1. Provide a differential diagnosis for thrombocytopenia in the nursery or NICU.

2. Discuss the management of thrombocytopenia in the neonate.

3. Explain the differences between thrombopoiesis in the neonate compared with older children.

4. Describe the difference between neonatal autoimmune and alloimmune thrombocytopenia.

5. Discuss acquired conditions of thrombocytopenia (eg, disseminated intravascular coagulopathy, thrombosis).


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ABBREVIATIONS

CAMT congenital amegakaryocytic thrombocytopenia
DIC disseminated intravascular coagulation
HPA human platelet antigen
ICH intracranial hemorrhage
IVIG intravenous immunoglobulin
NAIT neonatal alloimmune thrombocytopenia
NEC necrotizing enterocolitis
TAR thrombocytopenia–absent radii
WAS Wiskott-Aldrich syndrome
XLT X-linked thrombocytopenia
THROMBOPOIESIS IN THE NEWBORN

Platelets were first described as discrete particles “piastrine” by Italian physician Giulio Bizzozero; since then, we have learned a great deal about these molecules that are key for hemostasis and thrombosis. Megakaryocytes produce platelets in a complex process that is stimulated by thrombopoietin. In neonates, megakaryopoiesis starts with megakaryocyte precursors circulating in both the blood and bone marrow, rather than solely in the bone marrow as in adults. Megakaryocytes undergo a maturation process in which they increase their DNA content and develop polyplody (8N-64N). These mature megakaryocytes then generate and release new platelets into the circulation.

Megakaryocytes that have a higher ploidy produce more platelets. In the neonate, megakaryocytes generally are smaller in size and have lower ploidy. Many cytokines (interleukins 3, 6, 11) and chemokines (stromal cell–derived factor and fibroblast growth factor 4) are involved in megakaryopoiesis, but thrombopoietin is the most potent stimulator. Thrombopoietin is produced in the liver and has different effects on neonatal and adult megakaryocytes. Thrombopoietin stimulates polyplloidization in adult megakaryocytes, hence increasing platelet production. In the neonate, thrombopoietin inhibits polyplloidization, and megakaryocytes are even more sensitive to its stimulation. Because neonates have a normal platelet count, this means that the megakaryocytes and their progenitors have a very high proliferative potential to compensate the innate challenges of the neonatal megakaryocyte. Reticulated platelets are another emerging field of investigation in neonatal megakaryopoiesis. These are newly released platelets (24 hours old) that contain residual RNA and can be detected via flow cytometry. Another test, the percentage of the immature platelet fraction, is the percentage of reticulated platelets equivalent and is being investigated for clinical use to determine bone marrow response.

It is important to understand the differences between neonatal and adult megakaryopoiesis. One major distinction is that neonates lack reserve in their platelet production potential. Thus, when various causes lead to platelet consumption (eg, viruses, necrotizing enterocolitis [NEC], and disseminated intravascular coagulation [DIC]), the neonate can develop thrombocytopenia. This review will also discuss immune and nonimmune causes of thrombocytopenia.

DEFINITION AND INCIDENCE OF NEONATAL THROMBOCYTOPENIA

The presence of thrombocytopenia is highly variable in newborns, with the prevalence being significantly higher in sick infants. Thrombocytopenia is defined as a platelet count less than 150×10^3/μL (150×10^9/L). Overall, thrombocytopenia occurs in fewer than 1% of all newborns, but the highest prevalence occurs in the NICU (20%–35%), especially in very low-birthweight preterm neonates (70%–80%). Severe neonatal thrombocytopenia is typically defined as a platelet count less than 50×10^3/μL (50×10^9/L) and has been associated with significant clinical implications such as intracranial hemorrhage (ICH) and pulmonary or gastrointestinal bleeding.

Thrombocytopenia in preterm infants is very common and is frequently due to prenatal complications (pregnancy-induced hypertension, intrauterine growth restriction, placental insufficiency). In these situations, the platelet count usually is not in severe range (ie, typically greater than 50×10^3/μL [50×10^9/L]) and spontaneous resolution occurs by 2 weeks of age. Perinatally acquired infections (eg, cytomegalovirus, group B Streptococcus) and severe perinatal hypoxia are also frequent culprits, often associated with DIC. These perinatal insults typically cause thrombocytopenia within the first 72 hours of age. Postnatally acquired infections or complications such as NEC precipitate thrombocytopenia after 72 hours of age. Although term infants can also have thrombocytopenia from all of the aforementioned reasons, neonatal alloimmune thrombocytopenia (NAIT) is the most common cause of thrombocytopenia in a healthy full-term infant and usually resolves within a week. If thrombocytopenia persists for more than 7 to 10 days in the well infant, congenital abnormalities, bone marrow failure syndromes, and other disorders have to be included in the differential.

PLATELET FUNCTION AND GUIDELINES FOR PLATELET TRANSFUSIONS

Platelets are short-lived cells, with a half-life of 7 to 10 days. The primary function of platelets is to prevent bleeding by maintaining endothelial integrity and forming platelet aggregates. Hence, if platelets are not functioning properly or are decreased in number, the clinical manifestations are bleeding, bruising, or petechiae. The bleeding is primarily mucocutaneous, but ICH can occur, particularly in preterm infants.

National guidelines typically recommend platelet transfusions to maintain platelet counts greater than 20 to 50×10^3/μL (20–50×10^9/L); however, this is based on expert opinion and consensus evidence rather than prospective, randomized, controlled trials. For preterm infants, the concern for bleeding is even higher and the causes of thrombocytopenia are typically associated with a higher bleeding risk (eg, DIC, NEC, infection). While the goal of treating thrombocytopenia in a neonate is to prevent a life-threatening hemorrhage, there is little evidence showing that certain platelet thresholds will prevent bleeding. To our
knowledge, there is only 1 prospective study (Andrew et al) that investigated if transfusing platelets would decrease the incidence of ICH. The inclusion criteria for this study only involved very low-birthweight neonates with moderate thrombocytopenia \( (50–150 \times 10^3/\mu L) \) \( (50–150 \times 10^3/L) \) in the first week after birth and this degree of thrombocytopenia did not have a negative impact on the outcomes of intracranial bleeding. Guidelines to help the clinician with decision-making should be based on platelet count, health of the neonate, and bleeding history.

- In general, if a neonate has a platelet count that is less than \( 20 \times 10^3/\mu L \) \( (20 \times 10^9/L) \), the neonate should receive a platelet transfusion, regardless of age or clinical condition.
- If a neonate has a platelet count that is less than \( 30 \times 10^3/\mu L \) \( (30 \times 10^9/L) \), indications to transfuse platelets include weight less than 1 kg, age less than 1 week, clinical instability, history of major bleeding (eg, IVH), current active bleeding, coagulopathy/DIC, need for surgery or invasive procedures.
- If a neonate has a platelet count that is greater than \( 50 \times 10^3/\mu L \) \( (50 \times 10^9/L) \), recommendations are to transfuse platelets for significant bleeding only.

Further prospective studies are needed in neonates, including neonates with severe thrombocytopenia, to help clinicians determine the safest and most effective interventions in critically ill neonates.

### Causes of Thrombocytopenia and Approach to Thrombocytopenia in the Neonate

The causes of neonatal thrombocytopenia are broad and to determine the diagnosis, the clinician must consider the health of both the mother and infant, the infant’s gestational age, complications of delivery, the current clinical state of the neonate (healthy vs ill), and the severity of the thrombocytopenia. The Table reviews the differential diagnosis of neonatal thrombocytopenia. Thrombocytopenia can be caused by both inherited and acquired causes, and the diagnostic evaluation could be very extensive, so it is important to obtain the relevant information. Key factors that need to be considered are the onset of thrombocytopenia (early thrombocytopenia is defined as <72 hours of age and late thrombocytopenia is defined as >72 hours after birth), gestational age of the patient (term vs preterm), maternal history, severity of thrombocytopenia, the health status of the infant, family history of thrombocytopenia, and the presence or absence of congenital malformations. Figures 1, 2, and 3 have simplified algorithms of the approach to a differential diagnosis for preterm infants (based on early and late development of thrombocytopenia) and term infants.

Both term and preterm infants can become critically ill and develop thrombocytopenia as a result of consumption from complications such as infection, hypoxia, meconium aspiration, respiratory distress syndrome, NEC, and thrombosis. The sick newborn needs to be supported through the illness, receive platelet transfusion for indications that have been described before, and be evaluated to identify the underlying condition. If a sick neonate has a platelet count less than \( 50 \times 10^3/\mu L \) \((50 \times 10^9/L) \), sepsis, DIC, or NAIT, are all possible diagnoses. Thrombocytopenia will not resolve for at least 5 to 7 days until the underlying condition has resolved.

Mild thrombocytopenia \( (50–149 \times 10^3/\mu L) \) \((50–149 \times 10^9/L) \) often occurs following fetal distress from chronic intrauterine hypoxia. This is a broad category and the most common causes are pregnancy-induced hypertension and/or fetal intrauterine growth restriction. Neonatal thrombocytopenia associated with placental insufficiency is commonly from chronic intrauterine hypoxia and is evident immediately after birth; this can be accompanied by other hematologic abnormalities such as transient neutropenia and increased numbers of circulating nucleated red cells. The severity of the placental insufficiency directly correlates with the degree of thrombocytopenia, but usually the platelet count is greater than \( 50 \times 10^3/\mu L \) \((50 \times 10^9/L) \) and resolves within 14 days. If the degree of thrombocytopenia is more severe, or the recovery time is longer than expected, additional investigation is required. If there is no evidence of placental insufficiency, the neonatologist should ask about a family history of thrombocytopenia, check the maternal platelet count, and assess for any stigmata of a congenital syndrome such as thrombocytopenia–absent radii (TAR) syndrome, Fanconi anemia, trisomy 13, 18, 21, or Turner syndrome.

The most common reason for a healthy newborn to develop severe thrombocytopenia is NAIT, which is attributed to an immune-mediated destruction of fetal and neonatal platelets. Maternal antibodies cross the placenta to destroy fetal platelets expressing a paternal human platelet antigen (HPA) that the mother lacks. Other more rare causes of severe thrombocytopenia include vascular malformations and renal vein thrombosis.

The sections below include a brief overview of the most common causes of thrombocytopenia in newborns—immune-mediated (NAIT), abnormal production of platelets, or consumption of platelets due to acquired disorders (thrombosis, sepsis).

### Diagnosis and Management of NAIT

NAIT can have a dramatic presentation in an otherwise well neonate who has petechiae, bruising, and even significant bleeding (ICH). The pathophysiology includes an HPA
mismatch between the infant’s mother and father. In NAIT, fetal platelets that exhibit a paternal antigen that is distinct from the maternal platelet antigen cross the placenta and induce a maternal response with the production of maternal antiplatelet antibodies. These are immunoglobulin G antibodies, and can cross the placenta into the fetus, leading to platelet destruction and fetal and neonatal thrombocytopenia. NAIT typically leads to severe thrombocytopenia and up to 20% of neonates can have an ICH with 50% occurring in utero. It is crucial to diagnose NAIT because subsequent pregnancies can be affected. NAIT can develop in the first pregnancy of an at-risk couple and subsequent pregnancies can have even more significant bleeding.

The diagnosis of NAIT is made by demonstrating platelet antigen incompatibility between the mother and the neonate. This can be done in 2 ways: detection of maternal anti-HPA antibodies in the infant’s circulation or HPA genotype mismatch between the infant and mother. All children who are diagnosed with NAIT should have genotyping of both the mother and father. In white populations, 95% of NAIT occurs from a mismatch in HPA-1a or HPA-5b, and the remaining 5% is due to anti-HPA-2, -3 or -15. Black patients have a much higher gene frequency of HPA-2b and HPA-5b, while the incidence of HPA-1b is much lower than in whites. Additional research needs to be done to elucidate the differences in HPA across ethnicities.

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<tr>
<th>MECHANISM</th>
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<th>DIFFERENTIAL DIAGNOSES</th>
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<tr>
<td>Increased destruction of platelets</td>
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<td>Autoimmune thrombocytopenia (maternal immune thrombocytopenic purpura, systemic lupus</td>
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<td>erythematosis)</td>
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<td>Drug-dependent antibodies (penicillin and derivatives, vancomycin, metronidazole)</td>
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<td>Nectrotizing enterocolitis</td>
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<td>Vascular tumor (Kasabach-Merritt syndrome, hepatic hemangioidothelioma)</td>
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<td>Extracorporeal membrane oxygenation</td>
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<td>Decreased production of platelets</td>
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<td>Decreased production of platelets</td>
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<td>thrombocytopenia absent radii syndrome)</td>
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<td>Parasites</td>
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<td>Toxoplasmosis</td>
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All neonates with suspected NAIT should be screened for ICH with head ultrasonography because ICH can have significant neurologic sequelae. If a newborn’s platelet count is less than $3 \times 10^9/\mu L$ ($30 \times 10^9/L$) or if there are signs of bleeding, the ideal treatment for a neonate with NAIT is to provide HPA-1a-negative and 5b-negative platelets from the blood bank. Random donor platelets can be effective even though they will likely have the inciting antigen. Maternal platelets can only be used if they are washed because circulating antibodies will also be present.

In conjunction with platelet transfusions, intravenous immunoglobulin (IVIG) can be helpful in the management of NAIT in neonates. The proposed mechanism of action of IVIG in this disease involves inhibition of peripheral immune platelet destruction, but the pathophysiology has not been fully elucidated. After IVIG administration, it usually takes about 36 hours for the neonate to demonstrate a response in platelet count. Platelet counts need to be monitored until they return to normal levels. Infants with NAIT need to be followed by a hematologist after discharge from the NICU. If the mother is interested in becoming pregnant in the future, it is recommended that both she and her obstetrician be informed of the risks of NAIT in future pregnancies. During subsequent pregnancies, antenatal treatment of NAIT is important to decrease the risk of bleeding complications, especially because the majority of ICH occurs before birth. A recent systematic review by Winkelhorst et al suggests that first-line antenatal management is weekly maternal IVIG administration, with or without the addition of corticosteroids. There is a high complication rate (11%) of antenatal management with fetal blood sampling and intrauterine platelet transfusions, including fetal loss.

**DIAGNOSIS AND MANAGEMENT OF NEONATAL AUTOIMMUNE THROMBOCYTOPENIA**

Maternal autoantibodies arising from autoimmune conditions (immune thrombocytopenic purpura or systemic lupus erythematosus) can also cause thrombocytopenia in neonates because of the transplacental passage of maternal antibodies to the fetus. These antibodies typically do not cause the same degree of neonatal thrombocytopenia. Because the antibodies also affect maternal platelets, the mother’s platelet count is low. Family history can help to establish this diagnosis, but many women are asymptomatic.
and unaware of a potential disorder. If a pregnant woman has a known autoimmune condition associated with thrombocytopenia, a platelet count should be obtained on the infant after delivery. A neonate with thrombocytopenia associated with maternal autoimmune disease requires a supportive management approach; if there is severe neonatal thrombocytopenia or bleeding, IVIG and/or platelet transfusions may be needed.

**DECREASED PRODUCTION OF PLATELETS: INHERITED THROMBOCYTOPENIAS**

**Disorders of Small Platelets**

**Wiskott-Aldrich Syndrome and X-linked Thrombocytopenia.**

Wiskott-Aldrich syndrome (WAS) and X-linked thrombocytopenia (XLT) are both inherited X-linked microthrombocytopenia syndromes that are caused by mutations in the WAS protein (WASP) gene on the short arm of the X chromosome. The WAS protein is important in the cytoskeleton of megakaryocytes and T lymphocytes. WAS is a syndrome that is characterized by immunodeficiency, eczema, microthrombocytopenia, and development of autoimmune conditions and malignancy. Early recognition is important so that affected patients can be placed on bacterial and fungal prophylaxis. XLT is a less severe form of WAS and patients usually have isolated microthrombocytopenia. Genetic defects in the WAS gene that lead to absent or markedly decreased expression lead to the WAS phenotype, while individuals with missense mutations with partial expression of WAS have the XLT phenotype. Currently, the only cure for WAS is bone marrow transplantation, but small studies have shown eltrombopag, a thrombopoietin mimetic, can improve thrombocytopenia in patients with both WAS and XLT.

**Disorders of Normal-Sized Platelets**

1. **Congenital Amegakaryocytic Thrombocytopenia.** Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare recessive autosomal disorder that typically presents shortly after birth. Most affected infants have severe thrombocytopenia with petechiae, bruising, or bleeding. Most patients with CAMT have mutations in the c-mlp gene, the receptor for thrombopoietin, and hence, have a markedly reduced number of megakaryocytes. CAMT typically presents with isolated thrombocytopenia, but affected children are at high risk for developing complete bone marrow failure in the first few years of age. Bone marrow transplantation is currently the only curative option.

2. **TAR Syndrome.** This syndrome is characterized by bilateral absence of the radii and the presence of thrombocytopenia. Recently, 2 genetic mutations have been found in the majority of patients: microdeletion on chromosome 1q21 and 2 rare single nucleotide polymorphisms in the RBM8A gene. This syndrome results from impaired reactivity to thrombopoietin in the hematopoietic stem and progenitor cells, as well as megakaryocytes. The underlying pathophysiology to explain the association of thrombocytopenia and absent radii still needs to be elucidated. Severe thrombocytopenia occurs shortly after birth, and affected neonates frequently have bleeding. Other physical abnormalities have also been described in patients with TAR including cardiac, urogenital, and other skeletal abnormalities. In patients with TAR, both thumbs are present, in contrast to the skeletal abnormalities of children with Fanconi

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**Figure 3.** Differential diagnosis for thrombocytopenia (<150x10^3)/μL [150x10^9/L]) in full-term neonates. NAIT=neonatal alloimmune thrombocytopenia.
anemia, another bone marrow failure syndrome. In most children with TAR, the platelet count will improve after 2 years of age, even to almost normal values of $100 \times 10^9/\mu L$ ($100 \times 10^9/L$). Until resolution of the thrombocytopenia, affected patients require supportive treatment with platelet transfusions as needed.

In patients with Fanconi anemia with missing radii, the thumbs are also absent, which is an important morphologic difference between Fanconi anemia and TAR syndrome.

3. Familial Platelet Disorder with a Propensity for the Development of Acute Myelogenous Leukemia. This is a rare autosomal dominant disorder characterized by thrombocytopenia, aspirinlike functional platelet defect, and propensity to develop myelodysplastic syndrome and acute myelogenous leukemia. Mutations involving RUNX1 lead to arrest of megakaryocyte maturation with an expanding population of progenitor cells. A family history of myelodysplastic syndrome or acute myelogenous leukemia should raise suspicion for this disorder in a newborn with thrombocytopenia or significant bleeding.

### Disorders of Large Platelets

1. Bernard-Soulier Syndrome. Bernard-Soulier syndrome is caused by a deficiency of the GPIb/IX/V complex on platelets, which binds to von Willebrand factor. Mutations for this condition are on chromosomes 17, 22, and 3. A homozygous deficiency is characterized by severe thrombocytopenia, giant platelets, inability for ristocetin-induced platelet aggregation, and significant clinical bleeding. Heterozygotes may have milder macrothrombocytopenia and less bleeding. The diagnosis of Bernard-Soulier syndrome is confirmed by the absence of CD41a or GPPlb-IX-V on flow cytometry. Treatment for Bernard-Soulier syndrome is mostly supportive and platelet transfusions may be needed for life-threatening bleeding.

2. MYH9-Related Disorders. Nonmuscle myosin heavy chain type IIa (MYH9) mutations cause macrothrombocytopenia and are found in several different syndromes (May-Hegglin anomaly, Fechtner syndrome, Sebastian syndrome, and Ebstein syndrome). May-Hegglin anomaly is characterized by the presence of leukocyte Dohle-like inclusion bodies in the neutrophils and is a rare cause of fetal or neonatal ICH. The defect in May-Hegglin anomaly is in the MYH9 gene on chromosome 22q.

3. Acquired Consumptive Disorders: Kasabach-Merritt Syndrome. Kasabach-Merritt syndrome is a life-threatening consumptive coagulopathy in the presence of a rapidly enlarging vascular tumor. It usually presents in early infancy with a phenomenon of coagulopathy, DIC, and microangiopathy that is associated with a vascular malformation. Fifty percent of patients with a vascular tumor present with this phenomenon and it is important to start treatment early to prevent life-threatening hemorrhage or anemia. Treatment involves supportive care and aggressive management with steroids. Sirolimus, a mechanistic target of rapamycin inhibitor, has demonstrated significant improvements in high-risk patients with these vascular lesions.

### THROMBOTIC DISORDERS

The incidence of venous thromboembolism is rising, especially in the neonatal population. The incidence of venous thromboembolism in children has increased from 34 to 58 per 10,000 hospital admissions in recent years. Because of the need for central catheters and the increased complexity of neonatal care, the incidence of venous thromboembolism is even higher, at 75 per 10,000 hospital admissions in infants younger than 28 days. Heparin-induced thrombocytopenia and arterial thrombosis are increasing concerns, though still quite rare in pediatrics. Thrombocytopenia and renal failure should prompt investigation for a renal vein thrombosis with Doppler ultrasonography. Treatment for thrombotic conditions in a neonate can be complicated by consumption of platelets at the time of thrombosis, hence making treatment challenging.

### CONCLUSIONS

Neonatal thrombocytopenia is extremely common and has a broad differential. It is important to factor in the timing of the thrombocytopenia, prenatal and maternal history, severity of the thrombocytopenia, and overall health of the infant. Although infection is the most common reason for early neonatal thrombocytopenia in sick infants, NAIT is the most common cause for well children. Treatment of neonatal thrombocytopenia is mainly supportive. The mechanisms underlying thrombocytopenia in a neonate typically take several weeks to resolve and will need to be followed by a pediatrician. It is important to keep a broad differential, and a hematologist evaluation may be warranted for children with persistent thrombocytopenia.

### American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the normal pattern of platelet production and maturation.
- Know the causes and pathophysiology of neonatal thrombocytopenia and thrombocytosis.
- Know the clinical and laboratory manifestations and management of neonatal thrombocytopenia and thrombocytosis.
Suggested Readings


Thrombocytopenia in the Newborn
Kerry Morrone
NeoReviews 2018;19:e34
DOI: 10.1542/neo.19-1-e34

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://neoreviews.aappublications.org/content/19/1/e34