Approach to the Newborn Who Has Thrombocytopenia

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Objectives  After completing this article, readers should be able to:

1. List the platelet counts that represent mild, moderate, and severe thrombocytopenia.
2. List common causes of thrombocytopenia in sick neonates, preterm infants, and infants who have other medical conditions.
3. List the conditions characterized by physical abnormalities or dysmorphic features that commonly are associated with thrombocytopenia.
4. List potential causes of thrombocytopenia in healthy-appearing neonates.
5. Describe the clinical manifestations of and treatment for neonatal alloimmune thrombocytopenia.

Introduction

Platelet counts in healthy fetuses (mid-second trimester) and neonates are the same as in normal children and adults. Neonatal platelet counts of 100 to 150 × 10^3/µL (100 to 150 × 10^9/L) represent mild thrombocytopenia, platelet counts of 50 to 100 × 10^3/µL (50 to 100 × 10^9/L) are considered moderate thrombocytopenia, and levels less than 50 × 10^3/µL (50 × 10^9/L) are categorized as severe thrombocytopenia. Thrombocytopenia in newborns is a result of increased platelet consumption (infections, thrombosis, immune-mediated) or decreased platelet production. In many neonates, particularly sick preterm infants, both impaired megakaryopoiesis and accelerated platelet destruction may occur simultaneously.

Mild asymptomatic thrombocytopenia occurs in 1% of healthy term infants. Severe thrombocytopenia in term infants, however, is rare, and most affected infants usually are recognized because of hemorrhagic manifestations (petechiae, purpura, or frank bleeding). Any term neonate whose platelet count is less than 50 × 10^3/µL (50 × 10^9/L) should be evaluated to establish a cause.

In contrast to the rarity of thrombocytopenia in healthy term neonates, low platelet counts are noted commonly in sick infants who often are preterm. Up to 25% of infants admitted to the neonatal intensive care unit (NICU) have thrombocytopenia. Also, in contrast to term newborns who present with hemorrhagic manifestations, most cases of thrombocytopenia in the NICU are discovered accidentally when routine studies are completed on infants admitted for nonhematologic conditions. More than 50% of infants in the NICU have platelet counts of less than 100 × 10^3/µL (100 × 10^9/L), and 20% have platelet counts of less than 50 × 10^3/µL (50 × 10^9/L). The severe thrombocytopenia in these newborns most often is due to other disease processes.

As a practical matter, in the absence of bleeding, only cases of severe thrombocytopenia (<50 × 10^3/µL [50 × 10^9/L]) should be evaluated for a specific cause. This approach is justified because most cases of mild-to-moderate thrombocytopenia resolve within a few days without complications and usually without a causal diagnosis. Moreover, many studies have demonstrated that the risk for bleeding, particularly intraventricular hemorrhage, is significant only in neonates who have severe thrombocytopenia.

When assessing thrombocytopenia in a newborn, the answers to several different questions can focus the inquiry. Is the child a term or preterm infant? Is the baby ill- or healthy-appearing? Are other medical complications present? Are there any features suggestive of a congenital infection? Are there any congenital anomalies or dysmorphic...
features? Does the infant appear to be healthy aside from petechiae associated with the isolated thrombocytopenia?

Thrombocytopenia in Sick Neonates, Preterm Infants, and Those Who Have Other Medical Complications

Numerous conditions are associated with low platelet counts (Table). For example, newborns who suffer hypoxia or acidosis after birth trauma often have low platelet counts, as do those who experience intrauterine growth retardation and chronic hypoxia from placental insufficiency. The mechanism of thrombocytopenia in these cases may be hypoxic injury to fetal megakaryocytes. Because it is common to see increased numbers of nucleated red blood cells under these hypoxic conditions, an alternative explanation may be that the progenitor cell is driven toward the erythroid series at the expense of leukocytes and platelets. Neonatal cold injury from severe hypothermia can cause a thrombocytopenia that worsens upon rewarming.

Pre-eclampsia is a well-known cause of maternal thrombocytopenia, and the magnitude of thrombocytopenia usually correlates with the severity of pre-eclampsia. Newborns of affected mothers also can have thrombocytopenia, which occurs in approximately 1% of all pregnancies, especially among preterm infants. Affected neonates develop thrombocytopenia at birth and often have associated neutropenia. Platelet counts reach a nadir at approximately 4 days of age, rarely dropping below $50 \times 10^9$/mL ($50 \times 10^9$/L), and usually recovering to normal levels by 7 to 10 days of age. The exact mechanism of neonatal thrombocytopenia associated with maternal pre-eclampsia is not clear, although recent evidence suggests a possible disruption of hematopoietic progenitor cell commitment to megakaryocytopoiesis. Complications from prematurity (eg, infections, neonatal hypoxia, acidosis) also contribute to the thrombocytopenia in some of these children.

Infection is a frequent cause of thrombocytopenia in both term and preterm infants and should be ruled out in any ill-appearing newborn whose platelet count is less than $50 \times 10^9$/mL ($50 \times 10^9$/L). Bacterial sepsis causes thrombocytopenia by several mechanisms, including disseminated intravascular coagulation (DIC), endothelial damage, immune-mediated destruction, platelet aggregation due to bacterial products adhering to platelet membrane, and decreased platelet production from infected bone marrow. Viral infections in the perinatal period can cause severe thrombocytopenia, presumably a result of sialic acid loss from platelet membranes due to viral neuraminidase, intravascular platelet aggregation, and decreased production from degeneration of megakaryocytes. Congenital infections due to rubella and cytomegalovirus also are associated with thrombocytopenia via these mechanisms, but associated splenomegaly may play an additional role. Thrombocytopenia occasionally is the initial presenting feature of human immunodeficiency virus infection, but this usually occurs after several months of age and only rarely in the newborn period.

Thrombocytopenia also is a typical feature of DIC, which frequently complicates neonatal sepsis. Activation
of coagulation proteins leads to widespread fibrin deposition and consumption of platelets. In these cases, the prothrombin time, activated partial thromboplastin time, and thrombin clotting time are prolonged; fibrinogen concentration is reduced; and fibrin degradation products and D-dimers are present.

Preterm infants can develop complications commonly associated with thrombocytopenia, including respiratory distress syndrome (RDS), persistent pulmonary hypertension, and necrotizing enterocolitis (NEC). The increased platelet consumption in RDS and mechanical ventilation that often is required in those who have RDS also may play a role in the development of thrombocytopenia. In persistent pulmonary hypertension, there is evidence that intrapulmonary platelet aggregation and thromboxane A2 release from the platelets actually contribute to the hypertension. NEC is a frequent complication in preterm infants, especially among those whose birthweights are less than 1,500 g. Thrombocytopenia is found in 50% of infants who have NEC, and significant bleeding is common. In the early stage of NEC, the degree of thrombocytopenia correlates with the severity of bowel necrosis. Increasing platelet counts suggest improvement of the disease process.

Thrombosis causes neonatal thrombocytopenia by increased platelet consumption. The NICU population is at high risk for thrombosis due to increased susceptibility to DIC, the use of indwelling vascular catheters, and the use of extracorporeal membrane oxygenation. Exchange transfusions, another procedure that used to be performed frequently in the NICU, also can cause thrombocytopenia due to dilution.

Bone marrow disorders related to congenital malignancies (e.g., leukemia, neuroblastoma, or other solid tumors) and storage diseases can cause thrombocytopenia due to bone marrow infiltration by neoplastic cells or metabolic products. These rare disorders are distinguished by the presence of other physical findings (e.g., hepatomegaly, splenomegaly, and other palpable masses).

In each of the thrombocytopenic conditions described previously, the major focus should be on identifying and treating the underlying medical disorder. Platelet transfusions are used to treat bleeding symptoms and to lower the risks of serious hemorrhages. The specific indications for platelet transfusions differ according to gestational age. Generally, they are indicated in preterm and sick infants when the platelet count is less than $50 \times 10^3$/mL ($50 \times 10^9$/$L$) and in otherwise healthy term infants when the platelet count approaches $20 \times 10^3$/mL ($20 \times 10^9$/$L$).

## Thrombocytopenia in Neonates Who Have Physical Abnormalities or Dysmorphic Features

Thrombocytopenia with absent radius (TAR) syndrome is a rare autosomal recessive disorder characterized by severe thrombocytopenia present at birth and skeletal abnormalities of the radius (Table). Bilateral agenesis of radii is the most common skeletal anomaly, and thumbs always are present. Some affected patients also have congenital heart disease, particularly atrial septal defects and tetralogy of Fallot. All infants who have TAR syndrome present with profound thrombocytopenia (platelet count often $<10 \times 10^3$/mL [$10 \times 10^9$/L]) in the first week after birth. Risks for serious bleeding complications are greatest in the first months after birth. Platelet counts gradually improve over the first postnatal year and generally are normal after 1 to 3 years of age.

Fanconi anemia (FA) is a genetic form of aplastic anemia associated with a variety of congenital anomalies. The most common presenting hematologic feature is thrombocytopenia, but this rarely is a problem in the immediate newborn period. The congenital anomalies of FA, which are present at birth, most commonly include abnormalities of the hand with hypoplastic or absent thumbs and anomalies of the genitourinary system. Café au lait spots rarely may be seen in newborns; they usually appear later in the disease progression. The neonatologist should consider the possibility of FA and obtain appropriate diagnostic tests (chromosome breakage studies) for any newborn who has thumb abnormalities.

Chromosomal disorders due to trisomy 13, 18, or 21 and Turner syndrome also are associated with neonatal thrombocytopenia. These disorders are recognized by their individual clinical features.

Kasabach-Merritt syndrome is characterized by hemangiomas and thrombocytopenia. Coagulation is activated locally within the hemangiomas, and platelets are sequestered in the vascular malformation, leading to shortened platelet survival and thrombocytopenia. The full spectrum of this disorder rarely is present in newborns. The hemangioma lesions are notable at birth in 50% of patients who develop this syndrome, but the visceral hemangiomas may not be apparent on physical examination. In most instances, hemangiomas increase in size following birth, and significant thrombocytopenia ($<50 \times 10^3$/mL [$50 \times 10^9$/L]) with systemic bleeding occurs beyond the immediate newborn period.
Thrombocytopenia in Healthy-appearing Infants Who Have No Physical Abnormalities or Other Medical Conditions

Sometimes, healthy-appearing neonates who have thrombocytopenia may have an occult infection, including congenital viral infections, and these should be tested for even though the infant appears well (Table). Commonly, thrombocytopenia in otherwise healthy infants is due to immune-mediated platelet destruction caused by maternal antibodies that have crossed the placenta into the fetal circulation. Less commonly, healthy-appearing neonates who have thrombocytopenia may have a condition that is not expressed fully in the newborn period (eg, amegakaryocytic thrombocytopenia, hereditary macrothrombocytoid disorders, Wiskott-Aldrich syndrome).

Neonatal thrombocytopenia due to maternal autoimmune thrombocytopenia is primarily a maternal disorder that secondarily affects the fetus and newborn. Maternal idiopathic thrombocytopenic purpura (ITP) is a common cause of immune thrombocytopenia, but it also is seen in other autoimmune diseases, including systemic lupus erythematosus, lymphoproliferative disorders, and Graves disease. Maternal antibodies in these disorders are directed against “public” antigens on platelets, usually glycoproteins IIb/IIIa and Iib/IX. The immunoglobulin G antibody-coated platelets are cleared by the reticuloendothelial system, causing maternal thrombocytopenia. The fetus is affected because maternal antibodies cross the placenta and bind to the same public antigens on fetal platelets.

Maternal ITP is the most likely cause of moderate-to-severe thrombocytopenia (platelet count <70 × 10^9/mcL [70 × 10^9/L]) in otherwise healthy pregnant women. This must be distinguished from “benign gestational thrombocytopenia,” another common cause of mildly decreased platelet counts in otherwise healthy pregnancies. The latter is characterized by mild thrombocytopenia (platelet count >70 × 10^9/mcL [70 × 10^9/L]) in asymptomatic women who have no history of thrombocytopenia prior to pregnancy. It occurs in late gestation and generally resolves spontaneously after delivery. It is a benign disease for the mothers and does not cause thrombocytopenia in neonates.

Significant neonatal thrombocytopenia (platelet counts < 50 × 10^9/mcL [50 × 10^9/L]) occurs in fewer than 10% of cases of mothers who have ITP. When thrombocytopenia does occur, the platelet count generally is 20 to 50 × 10^9/mcL (20 to 50 × 10^9/L), and bleeding symptoms usually are mild. Neonatal autoimmune thrombocytopenia is diagnosed primarily according to a maternal history of thrombocytopenia and the clinical course of the neonate once other known causes of thrombocytopenia are excluded. An initial step in the evaluation of thrombocytopenia in healthy-appearing term infants is to determine the mother’s platelet count.

The general recommendation for obstetric management of mothers who have ITP is based solely on the risks of low platelets for the mother. No data are available to document that cesarean section is effective in reducing the very rare incidence of intracranial hemorrhage (ICH) in neonates who have thrombocytopenia. The course of immune thrombocytopenia in the mother does not predict outcome of the infant. Mothers who are stable postsplenectomy, with a current platelet count of less than 50 × 10^9/mcL (50 × 10^9/L) during the pregnancy, are at somewhat increased risk for having babies who have moderate thrombocytopenia. Fetal platelet count can be determined by percutaneous umbilical blood sampling at 38 weeks’ gestation or by scalp vein sampling during labor, although these interventions are not recommended. The risks associated with umbilical blood sampling are greater than the risk of ICH, and the platelet counts obtained by scalp vein generally are not reliable.

All infants born to mothers who have ITP should have a cord blood platelet count measured and be observed for any bleeding symptoms. For those who have severe thrombocytopenia (platelet count <20 × 10^9/mcL [20 × 10^9/L]) or clinical bleeding, intravenous immune globulin (IVIG) is indicated. A dose of 1 g/kg has been shown to be safe and effective in neonates, with a response rate of 80% to 90%. Platelet transfusions are less likely to be effective and should be used as an adjuvant treatment for those who exhibit severe bleeding symptoms. For affected neonates who have mild or moderate thrombocytopenia, platelet counts should be monitored daily because they often decrease following birth before generally recovering to normal levels by 7 to 14 days of age.

The clinical course of neonatal thrombocytopenia in infants born to mothers who have systemic lupus erythematosus is similar to that seen with ITP. The thrombocytopenia is mild, and serious bleeding (ICH) does not occur.

Neonatal alloimmune thrombocytopenia (NAIT) is the platelet equivalent of hemolytic disease of the newborn due to red blood cell Rh D incompatibility. It occurs when a mother lacks a platelet antigen that her fetus has inherited from the father. Maternal immunoglobulin G antibodies form against the “foreign” antigen on fetal platelets, cross the placenta, and destroy fetal platelets. NAIT can result in severe thrombocytopenia,
and affected fetuses and neonates are at high risk for serious bleeding complications. There are no maternal consequences. Unlike Rh hemolytic disease, 50% of NAIT cases occur in the first pregnancy of an at-risk couple.

The most commonly identified antibody in sensitized Caucasian women is anti-human platelet antigen-1a (HPA-1a), formerly known as PlA1. This antiplatelet antibody accounts for 80% to 90% of NAIT cases. The HPA-1a platelet antigen is found in 98% of Caucasians. The predicted frequency of fetomaternal alloimmunization with HPA-1a is estimated to be 1 in 350 pregnancies, although the actual incidence of clinically apparent NAIT is about 1 in 3,000 pregnancies. The fact that only 10% of HPA-1a negative women exposed to HPA-1a become sensitized is determined by other immune response genes. Increased alloimmunization to HPA-1a is seen in women who have human leukocyte antigen (HLA)-B8, HLA-DR3, and HLA-DR52a. In 5% to 15% of NAIT cases, the responsible antibody is anti-HPA-5b (formerly Brh). Among Asians, NAIT occurs with sensitization to HPA-4 (formerly Yuk/Pen). NAIT also occurs with maternal HLA antibodies alone or in combination with HPA antibodies. HLA antibodies, though common, usually do not cause significant thrombocytopenia because other tissues also can absorb these antibodies, thus sparing platelets.

Clinical manifestations of NAIT vary from mild-to-moderate thrombocytopenia in a healthy-appearing infant to severe thrombocytopenia with bleeding complications. The platelet count commonly falls further during the first week after birth. The most serious complication of NAIT is ICH, which is estimated to occur in approximately 10% to 20% of affected newborns. Importantly, more than 25% of the ICH events occur in utero. NAIT should be suspected in any healthy newborn who has unexpected and unexplained severe thrombocytopenia and whose mother has a normal platelet count and no history of ITP or of having had a splenectomy for ITP in the past. The evaluation should include maternal antiplatelet antibody testing, although sometimes no circulating antibodies are found in maternal serum in presumed NAIT cases. It is for this reason that platelet antigen testing of both parents also is important in the diagnostic evaluation. The recurrence rate of NAIT is greater than 75% in subsequent pregnancies, and generally the thrombocytopenic course is more severe in subsequently affected children.

Management of NAIT depends on the gestational age of the infant, the severity of thrombocytopenia, whether there is any bleeding, and if there are any additional risk factors for bleeding. Infants who have mild or moderate thrombocytopenia (platelet count >20 × 10^9/mcL [20 × 10^9/L] in term and >50 × 10^9/mcL [50 × 10^9/L] in preterm infants) and no sign or risk factor for bleeding can be observed, with daily platelet counts measured until they begin to rise. Besides following the platelet count, cranial ultrasonography should be obtained to rule out ICH. Those who have severe thrombocytopenia (platelet count <20 × 10^9/mcL [20 × 10^9/L] for term and <50 × 10^9/mcL [50 × 10^9/L] for preterm infants) and any bleeding or risk factors for bleeding (prematurity or need to undergo invasive procedure) should be treated. The primary treatment for NAIT is platelet transfusion with either washed maternal platelets or HPA-compatible platelets. For those in whom NAIT is suspected but for whom the diagnostic evaluation is not yet complete, platelets negative for HPA-1a and HPA-5b can be administered, if available. The platelets also should be cytomegalovirus-negative and irradiated. If compatible platelets are not readily available, IVIG with or without random donor platelets can be used. IVIG is useful in this disorder just as with thrombocytopenia due to maternal immune thrombocytopenia.

Once the diagnosis of NAIT is established, parents need to be counseled regarding the risks and management of future pregnancies. They should be referred to obstetricians who specialize in managing high-risk pregnancies. The best predictor for the degree of fetal thrombocytopenia in the future is the disease severity of a previously affected infant in the same family. There are no reliable noninvasive methods for monitoring and managing affected pregnancies. Treatment options include serial measurement of fetal platelet counts by percutaneous umbilical cord sampling starting at 20 weeks’ gestation. In those fetuses that exhibit significant thrombocytopenia, weekly IVIG can be administered to mothers with or without in utero platelet transfusions. Delivery by cesarean section is recommended.

Congenital amegakaryocytic thrombocytopenia is a rare autosomal recessive disorder that causes severe neonatal thrombocytopenia. Affected children often present in infancy with bleeding symptoms (petechiae and mucosal and gastrointestinal bleeding). Subgroups of children also have congenital anomalies (cardiac defects, abnormal facies, microcephaly). Bone marrow examination reveals a paucity of megakaryocytes, but is otherwise normal. Thrombocytopenia progresses to pancytopenia in later childhood, and progression to leukemia has been reported in a few cases. Bone marrow transplant is the only curative treatment.

Hereditary macrothrombocytopenias are a group of
autosomal dominant disorders caused by mutations in the MYH9 gene. Collectively, these disorders include May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome. They are characterized by mild-to-moderate thrombocytopenia with giant platelets (mean platelet volume, 30 to 80 fL). Neutrophil inclusions (Dohle bodies), nephritis, and deafness are seen in some of these disorders. In most cases, these thrombocytopenic disorders are not associated with a significant bleeding tendency.

Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder characterized by immunodeficiency, eczema, and thrombocytopenia. A unique hematologic feature is smaller-than-normal platelets. The syndrome is caused by mutation of the WAS protein on the short arm of chromosome X. Affected children have thrombocytopenia and small platelet size at birth. In addition, the platelets in WAS do not function properly. Gastrointestinal bleeding is seen commonly and may be the presenting symptom. Symptoms associated with the immune dysregulation (frequent infections, eczema, autoimmune phenomena) generally become more apparent with time. The diagnosis is confirmed by determining WAS protein expression by flow cytometry. Bone marrow transplant is the only curative treatment.

**Summary**

Thrombocytopenia often is encountered in newborns, particularly sick preterm infants. The useful initial assessment for neonates who have low platelet counts is based on whether they are sick because of other medical conditions or events. In these cases, thrombocytopenia often is discovered accidentally and is one of many complications. Alternatively, some neonates who have thrombocytopenia appear healthy aside from variable degrees of cutaneous and other hemorrhages. In these latter cases, it is particularly useful to consider whether there are associated dysmorphic features.

**Suggested Reading**


NeoReviews Quiz

12. A 780-g female infant is delivered at 30 weeks' gestational age by cesarean section prompted by fetal distress. The maternal history is significant for hypertension and proteinuria, and spontaneous rupture of membranes occurred 24 hours prior to delivery. The infant has Apgar scores of 2 and 4 at 1 and 5 minutes, respectively; a core body temperature of 94.6°F (34.8°C); and clinical and radiographic evidence of hyaline membrane disease. Her blood count reveals: hemoglobin, 18 g/dL (180 g/L); total leukocyte count, 3.5 x 10³/mcL (3.5 x 10⁹/L); and platelet count, 28 x 10³/mcL (28 x 10⁹/L). Of the following, the most likely cause of severe thrombocytopenia in this infant is:

A. Hyaline membrane disease.
B. Hypothermia.
C. Maternal preeclampsia.
D. Neonatal sepsis.
E. Perinatal asphyxia.

13. Neonatal thrombocytopenia, accompanied by physical abnormalities or dysmorphic features, is a frequent manifestation of an inherited genetic disorder. Of the following, the most likely syndrome in an infant who has thrombocytopenia and thumb anomalies is:

A. Down syndrome.
B. Fanconi syndrome.
C. Kasabach-Merritt syndrome.
D. Thrombocytopenia with absent radius syndrome.
E. Turner syndrome.

14. Neonatal alloimmune thrombocytopenia is mediated by maternal antibodies directed against antigens on fetal platelets. These platelet antigens are designated as human platelet antigens (HPAs) 1 to 9, and the different allelic forms are distinguished by the suffix a or b. Of the following, the most common human platelet antigen responsible for neonatal alloimmunization in infants of Asian heritage is:

A. HPA-1b.
B. HPA-2a.
C. HPA-3b.
D. HPA-4a.
E. HPA-5b.

15. Thrombocytopenia in a healthy-appearing neonate may be caused by an inherited disorder that is not fully expressed in the newborn period. The platelets in these disorders, in addition to being reduced in number, may be altered in structure and function. Of the following, the inherited disorder most likely to be associated with platelets that are much smaller than normal is:

A. Epstein syndrome.
B. Fechtner syndrome.
C. May–Hegglin anomaly.
D. Sebastian syndrome.
E. Wiskott–Aldrich syndrome.