Neonatal Thrombocytopenia

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Drs Fernández and de Alarcón have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational 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 a variety of congenital or acquired conditions in the neonatal period and prompt further diagnostic evaluations.

Abstract

Thrombocytopenia is one of the most common hematologic problems in the neonate. It affects up to 30% of all patients admitted to the neonatal intensive care unit (NICU). The causes of thrombocytopenia in neonates are diverse and include immune, inherited, and acquired disorders. The evaluation of the neonate with thrombocytopenia may be challenging. Developing a diagnostic strategy to evaluate the neonate with thrombocytopenia is key for the practicing clinician. Here, we provide a practical approach to the evaluation of the neonate with thrombocytopenia and an overview of its most common etiologies.

Objectives

1. Describe the differences between neonatal and adult thrombopoiesis.
2. Provide a differential diagnosis of neonatal thrombocytopenia.
3. Describe the clinical presentation and management of the most common forms of thrombocytopenia during the neonatal period.
4. Explain and contrast the pathophysiology of neonatal autoimmune thrombocytopenia and alloimmune thrombocytopenia.
5. Describe the most common inherited causes of thrombocytopenia in the newborn.
6. Discuss the approach to treatment for the neonate with thrombocytopenia according to the etiology.

Abbreviations:

BSS: Bernard Soulier syndrome
CAMT: congenital amegakaryocytic thrombocytopenia
DIC: disseminated intravascular coagulation
FA: Fanconi anemia
GP: glycoprotein
HPA: human platelet antigen
ICH: intracranial hemorrhage
IVIG: intravenous immunoglobulin
NAIT: neonatal alloimmune thrombocytopenia
NEC: necrotizing enterocolitis
NICU: neonatal intensive care unit
TAR: thrombocytopenia absent radii
Tpo: thrombopoietin
WAS: Wiskott-Aldrich syndrome

Definition and Incidence

Thrombocytopenia is defined as a platelet count under 150,000/μL. However, healthy neonates tend to have platelet counts in the range of 100 to 150,000/μL. Thrombocytopenia occurs in less than 1% of all neonates, but is one of the most common hematological problems in neonates, affecting 25% to 30% of all admissions to the neonatal intensive care unit (NICU). The evaluation and management of thrombocytopenia is a challenge for the neonatologist and hematologist, because it can be caused by multiple disease processes. Therefore, a review of the differential diagnosis, the pathophysiology, and the management of the newborn with thrombocytopenia is important.

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Platelets Production in the Newborn

Platelets are tiny cellular fragments produced by megakaryocytes. Platelet production, or thrombopoiesis, is a complex process that consists of four main steps:

1. Production of thrombopoietin (Tpo) as the thrombopoietic stimulus.
2. Generation and proliferation of megakaryocyte progenitors.
3. Maturation of megakaryocytes characterized by a progressive increase in nuclear ploidy (the number of sets of chromosomes in a given cell) and cytoplasmic maturity that leads to the generation of large polyploid (8N–64N) megakaryocytes.
4. Platelet formation and release of new platelets into the circulation.

These mechanisms are significantly different between neonates and adults with thrombocytopenia. In neonates Tpo levels are not as high in thrombocytopenic neonates, particularly in the small for gestational age infants, as those found in children or adults. The number of megakaryocyte progenitors circulating in the peripheral blood of neonates is higher than in children and adults. They give rise to colonies with a greater number of megakaryocytes, and may be more sensitive to Tpo stimulation in comparison with those of children or adults. Megakaryocytes in the neonate are smaller and have lower ploidy, but their cytoplasm reflects that of a mature cell. Last, Tpo effect inhibits megakaryocyte polyploidization in the neonate. Neonates maintain normal platelet counts on the basis of the increased proliferative potential of their megakaryocyte progenitors.

Most cases of thrombocytopenia encountered in the NICU are nonimmune and associated with several common neonatal conditions, such as chronic intrauterine hypoxia, sepsis, necrotizing enterocolitis (NEC), and viral infections. Although an in-depth review of the particular mechanism underlying the etiology of these nonimmune causes of thrombocytopenia in the neonate is beyond the scope of this review, understanding the differences between neonatal and adult megakaryopoiesis helps us see what predisposes the neonate to develop thrombocytopenia and the potential utility of thrombopoietic growth factors as potential therapeutic interventions in selected neonates.

Platelet Count and Risk of Bleeding

Circulating platelets are about one fifth of the diameter of a red blood cell, with a mean volume between 7 and 9 fL. Platelets live for a very short time in the circulation with a half-life of 7 to 10 days. Their primary function is to maintain the integrity of the vascular endothelium and to control hemorrhage from small-vessel injury through the formation of small aggregates or plugs in the microcirculation. Bleeding tendency results when platelets are deficient in number or function.

The normal platelet count in newborns and infants is considered to be between 150,000 and 450,000/μL. However, this range of platelet count comes from a limited number of small sample studies of healthy newborns. A study from 18 hospitals in the United States using data from more than 47,000 neonates reported lower limit of platelet ranges from neonates at various gestational ages during their first 90 days after birth of 123,000/μL in late preterm and term neonates and 104,000/μL in infants of less than 32 weeks' gestation. Whether or not a platelet count below 150,000/μL is considered abnormal, it should always be interpreted within the context of the clinical situation.

The tendency to bleed is proportional to the number of platelets within the circulation. As such, there is no risk of bleeding with platelet counts greater than 100,000/μL, minimal or mild risk of bleeding occurs with platelet counts between 20,000 and 100,000/μL, the risk is moderate with platelet counts below 20,000/μL, and the risk is severe and/or there is spontaneous bleeding with platelets below 5,000/μL. In the neonate, the correlation of platelet count with bleeding has not been established. The trauma and the stress of birth can precipitate, although rarely, intracranial or internal bleeding when platelets are below 30,000/μL, and, therefore, clinicians act upon this platelet count to prevent bleeding in the NICU setting. This threshold seems to be higher for preterm infants. Many centers will use a platelet count of 50,000/μL to transfuse preterm infants. However, there is little evidence that this approach will prevent intracranial hemorrhage (ICH). Prospective studies are warranted to establish the most safe and cost-effective threshold at which to transfuse premature infants.

The bleeding pattern in the presence of moderate to severe thrombocytopenia is mucocutaneous. The presence of petechiae, bruises, or bleeding from the mucous membranes is characteristic of low platelet counts. In the neonate, intraventricular hemorrhage or intracranial bleed are also possible in the setting of thrombocytopenia.

Diagnostic Approach to Neonatal Thrombocytopenia

Multiple disease processes can cause thrombocytopenia. A practical approach to the diagnosis and management of thrombocytopenia in the neonate can be based on the time of onset of thrombocytopenia (early ≤72 hours

after birth or late ≥72 hours after birth), gestational age of the patient (term versus preterm), on the underlying mechanism (consumption, increased destruction, decreased production), or on whether the thrombocytopenia is due to maternal or infant factors or individualized to the particular infant. Critical parameters that are common to all these approaches include the severity of thrombocytopenia, the maternal history, the health status of the infant, and the presence or absence of congenital malformations.

A simplified approach to the diagnosis of thrombocytopenia in the newborn is presented here. It is based on an algorithm (see Figure) and a table (see Table) that takes the above factors into account, especially the severity of thrombocytopenia and the level of illness of the neonate.

The sick newborn may become thrombocytopenic from a variety of neonatal complications such as infection, asphyxia, meconium aspiration, respiratory distress syndrome, polycythemia, NEC, and the presence of an indwelling umbilical catheter. In the sick newborn who has severe thrombocytopenia, specific treatment for the underlying condition should be provided and the thrombocytopenia treated symptomatically.

In general, mild to moderate thrombocytopenia with a platelet count between 50,000 and 149,000/μL in a healthy newborn that occurs in the first 72 hours after birth is associated with a maternal history of placental insufficiency. These infants will recover a normal platelet count within 10 days and require only close observation. In sick newborns without evidence of placental insufficiency, evaluation for sepsis is warranted in addition to initiation of broad spectrum antibiotics.

When the newborn's underlying condition improves, the thrombocytopenia should also improve, usually within 5 to 7 days. Persistent thrombocytopenia should alert the physician to look for other causes.

Patients with severe thrombocytopenia or a platelet count lower than 50,000/mL should be evaluated for sepsis, disseminated intravascular coagulation (DIC), or neonatal alloimmune thrombocytopenia (NAIT). If any of those are present no additional evaluation is required.

In newborns without signs of sepsis, additional evaluation must be pursued and must include: (1) maternal history of thrombocytopenia, (2) detailed familial history of thrombocytopenia, (3) detailed physical examination with special attention to the upper extremities, dysmorphic features suggestive of a congenital anomaly or a particular syndrome, such as thrombocytopenia-absent radii syndrome, Fanconi anemia, trisomy 13, 18, 21, or Turner syndrome.

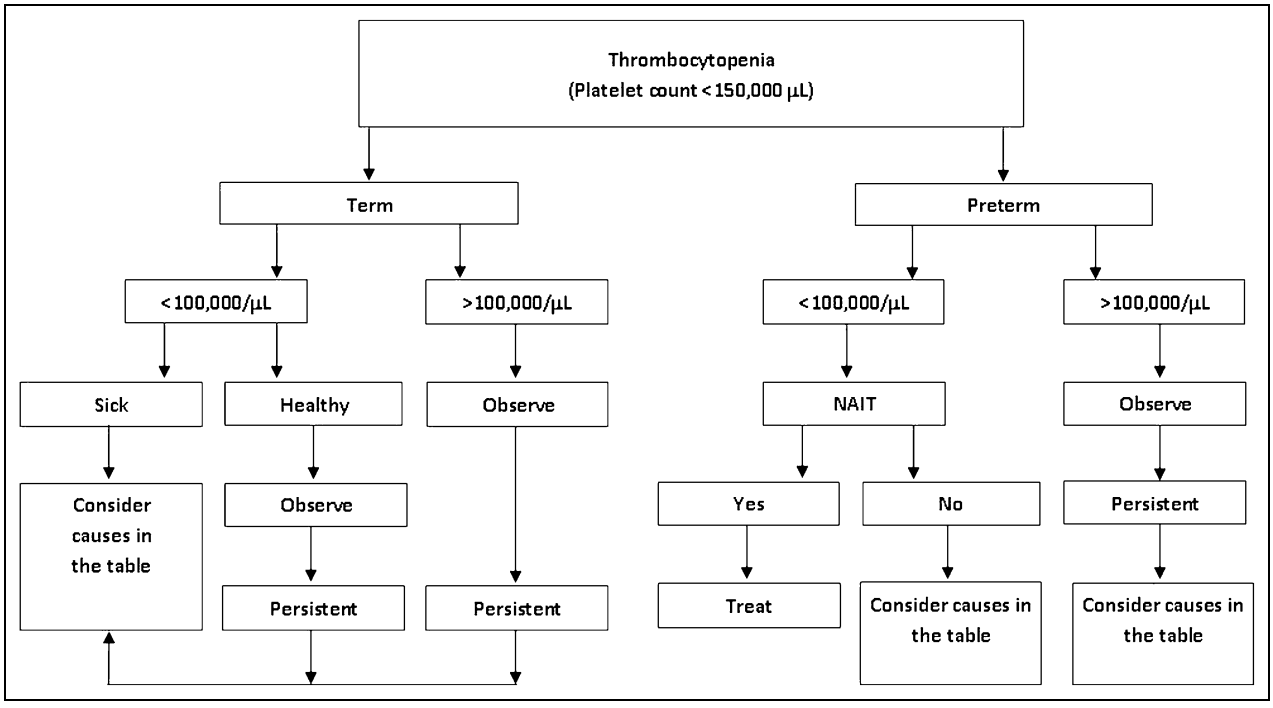

Figure. Diagnostic approach to an infant with thrombocytopenia. NAIT=Neonatal alloimmune thrombocytopenia.

Table. Specific Illnesses and Patterns Associated With Neonatal Thrombocytopenia

Categories	Subtypes	Differential Diagnoses (Where Applicable)	Severity	Onset
Immune	Alloimmune	Neonatal alloimmune thrombocytopenia	Severe	Early
	Autoimmune	Maternal ITP, lupus, other collagen vascular disorder	Severe-moderate	Early
Infectious	Bacterial	GBS, Gram-negative rods, *Staphylococcus*, etc.	Variable	Variable
	Viral	CMV, HSV, HIV, enteroviruses	Variable	Usually early
	Fungal	*Candida*, other	Severe	Usually early
	Parasite	Toxoplasmosis	Variable	Early
Placental insufficiency		Preeclampsia, eclampsia, chronic hypertension	Mild-moderate	Early
		Intrauterine growth restriction due to placental insufficiency	Mild-moderate	Early
DIC		Asphyxia	Severe	Early
		Sepsis	Severe	Variable
		Congenital TTP (rare)	Severe	Variable
Genetic disorders	Chromosomal	Trisomy 13, Trisomy 18, Trisomy 21, Turner syndrome, Jacobsen syndrome	Variable	Early
	Familial	Macrothrombocytopenias, Wiskott-Aldrich syndrome, X-linked thrombocytopenias, Amegakaryocytic thrombocytopenia, TAR, Fanconi anemia[a]	Variable	Early*
	Metabolic	Proprionic acidemia, methylmalonic acidemia, etc.	Mild-moderate	Variable
Medication induced	Antibiotics	Penicillin and derivatives, vancomycin, metronidazole, etc.	Variable	Late
	Heparin		Variable	Late
	Anticonvulsants	Phenytoin, phenobarbital	Variable	Late
	H_2 receptor antagonists		Variable	Late
Miscellaneous	Thrombosis	RVT, line-associated thrombosis, sagittal sinus thrombosis	Moderate	Variable
	Vascular tumor	Kasabach Kasabach-Merritt, hepatic hemangioendothelioma	Moderate	Variable
	NEC		Severe-moderate	Usually late
	ECMO		Variable	Variable

Most familial thrombocytopenias are present at birth except for Fanconi anemia, which usually does not appear until childhood. GBS=Group B streptococcus; ITP=immune thrombocytopenic purpura; CMV=cytomegalovirus; HSV=herpes simplex virus; HIV=human immunodeficiency virus; TTP=thrombotic thrombocytopenic purpura; TAR=thrombocytopenia-absent radii syndrome; RVT=renal vein thrombosis; NEC=necrotizing enterocolitis; ECMO=extra corporeal membrane oxygenation.

[a]Reproduced with permission from Fernández KS, de Alarcón PA. Congenital thrombocytopenias and thrombocytopathies. In: de Alarcón PA, Christensen RD, Werner EJ, eds. *Neonatal Hematology: Pathogenesis, Diagnosis, and Management of Hematologic Problems.* 2nd ed. Cambridge, United Kingdom: Cambridge University Press; 2013, p. 174.

In newborns with a negative maternal or familial history and an unrevealing physical examination, other infections, such as toxoplasmosis, other viruses and syphilis, rubella, cytomegalovirus, and human immunodeficiency virus complex; human immunodeficiency virus infection; or enteroviruses, should be considered. In addition, catheter-related thrombosis, chromosomal anomalies, and inborn errors of metabolism, especially propionic acidemia and methylmalonic acidemia, should be considered.

The most common etiology of severe thrombocytopenia in an otherwise healthy-looking newborn is immune-mediated thrombocytopenia in which there is passage of maternal antibodies from the mother to the fetus. Other rarer disorders, such as vascular tumors or hemangiomas with Kasabach-Merritt phenomenon and renal vein thrombosis, should be investigated.

When thrombocytopenia occurs more than 72 hours after birth, it is more likely to be due to bacterial or fungal

sepsis and/or NEC. For patients in whom a bacterial or fungal process is excluded as etiology of thrombocytopenia, viral infections such as herpes simplex virus and cytomegalovirus, DIC, catheter-related thrombosis, drug-induced thrombocytopenia, heparin-induced thrombocytopenia, or other inherited disorders should be considered. This group of patients constitutes the most common reason for consultation to the hematology team. Immune-mediated thrombocytopenias should also be considered in this group, in particular, because they tend to worsen in the first few days after birth. The differential diagnosis of immune-mediated thrombocytopenias is between NAIT, maternal autoimmune disorders, or, rarely, maternal drug-induced immune thrombocytopenia.

In the following sections we will highlight some of the features of the most common causes of thrombocytopenia in newborns in the three major categories of destruction of platelets by immune mediated process, decreased or abnormal production of platelets owing to inherited disorders, and consumption of platelets related to some acquired disorders.

Immune-Mediated Causes of Neonatal Thrombocytopenia

Neonatal Alloimmune Thrombocytopenia

NAIT is a rare disorder that presents in an otherwise well-appearing newborn with moderate to severe thrombocytopenia. NAIT occurs when fetal platelets contain an antigen inherited from the father, a human platelet antigen (HPA) that the mother lacks. Fetal platelets that cross the placenta into the maternal circulation trigger the production of maternal antiplatelet antibodies against the foreign antigen. These antibodies cross the placenta into the fetal circulation and destroy platelets resulting in fetal and neonatal thrombocytopenia. There are sixteen HPAs identified but only three cause 95% of the NAIT cases (HPA-1a, HPA-5b, and HPA-15b). Feto-maternal incompatibility for HPA-1a is responsible for 75% of cases in whites. HPA-1a incompatibility occurs in 1:350 pregnancies, although thrombocytopenia develops in only 1:1,000 to 1,500 pregnancies.

Infants with NAIT will have symptoms of mucocutaneous bleeding but will look otherwise healthy. Typically, platelet count falls below 50,000 in the first few days after birth, but then rises as the alloantibody concentration declines, which usually happens in 1 to 4 weeks, the expected half-life of immunoglobulin G. This immune-mediated platelet disorder is the equivalent to Rh sensitization of red blood cells with the only difference that NAIT often develops in the first pregnancy of an at-risk couple. The most serious complication of NAIT is ICH. This may occur in as many as 10% of the cases, and up to 50% of the time it happens before birth. All infants with severe thrombocytopenia due to NAIT should have a cranial ultrasound to look for evidence of ICH.

If available, the best alternative to treat these patients is the use of HPA-1a–negative platelets from the blood bank. Random donor platelets, even though they are likely to have the target antigen, are effective in treating the infant with severe thrombocytopenia. Platelets obtained from the mother are also effective, but these platelets need to be washed to minimize the presence of the circulating anti-HPA-1a antibodies. Specific platelet antigen and antibody testing are not readily available at all centers but can be requested at major referral laboratories. The administration of intravenous immunoglobulin (IVIG) may be helpful and represents another alternative treatment but less effective than platelet transfusions. Once an infant is diagnosed with NAIT, it is important to carry out a complete diagnostic plan with genotyping of mother and father to be able to provide genetic counseling. In subsequent pregnancies, if the father is a homozygote for the affected antigen, therapy should be started as early as the 13th week of pregnancy with weekly IVIG with or without prednisone, depending on the severity of the previously affected infant or if there was a history of ICH. If the father is a heterozygote for the antigen, the risk of the infant must be determined by molecular analysis of fetal cells circulating in the maternal blood, if available, or by invasive procedures: chorionic villi biopsy or amniocentesis, which both carry significant risks to the pregnancies, to establish if the fetus is affected.

Neonatal Autoimmune Thrombocytopenia

Neonatal autoimmune thrombocytopenia, in contrast to NAIT, is caused by the passage of maternal antibodies that react with both maternal and infant platelets, and therefore both mother and infant are affected. This disorder occurs in maternal autoimmune disorders such as immune thrombocytopenic purpura or systemic lupus erythematosus. It occurs in 1 to 2:1,000 pregnancies. The diagnosis becomes obvious from a maternal history of thrombocytopenia. Transplacental passage of maternal autoantibodies in this setting is much less of a clinical problem than NAIT. It is important to note that the maternal history is not always positive, because there are many thrombocytopenic mothers who would be asymptomatic and therefore unaware of their own disorder. All neonates of mothers with autoimmune diseases should have their platelet count determined at birth. In most

cases, the platelet count rises spontaneously by day 7. In cases of severe thrombocytopenia, treatment with IVIG is recommended. The presence of unexplained thrombocytopenia in a newborn that is suggestive of autoimmune destruction and in whom NAIT has been excluded should trigger evaluation for the presence of an autoimmune disorder in the mother, because neonatal thrombocytopenia can sometimes be the presenting sign of maternal disease.

Inherited Thrombocytopenias

Aneuploidies

Thrombocytopenia is seen in neonates with trisomy 13, 18, and 21, and also with Turner syndrome. The exact mechanism of thrombocytopenia is unknown, but may be due to reduced platelet production and the pathogenesis may be similar to that seen in chronic fetal hypoxia.

Bernard–Soulier Syndrome

Bernard-Soulier syndrome (BSS) is a moderate to severe platelet function defect characterized by mild thrombocytopenia, giant platelets, and mucosal type bleeding. It is a very rare disorder with an incidence of 1:1,000,000. It may present in the neonatal period, although bleeding is not usually severe. It is a qualitative platelet disorder with a defect in the von Willebrand factor receptor, the glycoprotein (GP) complex GP Ib–IX–V.

The defect in BSS is in the GPIbα gene, and also in the GPIbβ and GPIX genes, mapped to chromosome 17, chromosome 22, and chromosome 3, respectively. Defect in chromosome 22 and abnormality in GPIbβ explains why infants with DiGeorge syndrome and cardiac disease may develop severe bleeding due to a coexisting BSS.

The diagnosis of BSS is confirmed by the absence of CD41a or PGPIb–IX–V by flow cytometry. Treatment for BSS is mostly supportive and with platelet transfusion for life-threatening bleeding. Mothers with BSS may develop alloantibodies against GPIb–IX–V that can cross the placenta, and, therefore, their offspring can develop NAIT due to the passage of alloantibodies against GPIb–IX–V antigens.

Wiskott–Aldrich Syndrome

Small platelets on peripheral blood film and/or a low mean platelet volume may indicate Wiskott–Aldrich syndrome (WAS). WAS is due to mutations in the WAS protein gene on the short arm of the X chromosome. Mutations in this gene have been isolated to Xp11.23. WAS is characterized by microthrombocytopenia, eczema, and recurrent bacterial and viral infections. Most cases will not present during the neonatal period unless there is a known family history. The disorder usually presents in the first year after birth with bleeding symptoms. Bleeding is due to abnormal platelet function, reduced platelet survival, and thrombocytopenia. X-linked thrombocytopenia is a part of the spectrum of WAS. These patients have thrombocytopenia and small platelets as the major manifestations of their disease. However, the difference is in the variable and less severe degrees of eczema and immunodeficiency.

Fanconi Anemia

Fanconi anemia (FA) can present in the newborn with persistent thrombocytopenia. It is, in most cases, an autosomal recessive disorder. The infant may present with thrombocytopenia alone, pancytopenia, or with dysmorphic features only. The associated congenital abnormalities of hypopigmented and hyperpigmented skin lesions, microcephaly, small size, urinary-tract abnormalities, and upper-extremity radial-side abnormalities involving the thumb, should alert the physician to the possibility of FA. The cross-linking agent diepoxybutane has been used effectively to diagnose FA and is the standard diagnostic test. Treatment is rarely necessary in the neonatal period.

Thrombocytopenia Absent Radii Syndrome

This syndrome is characterized by the bilateral absence of the radii and thrombocytopenia. The inheritance pattern of the thrombocytopenia absent radii (TAR) syndrome is autosomal recessive. Both boys and girls are affected, but there is a predominance of girls. The onset of symptoms usually occurs very early in life. Half of the patients have onset of hemorrhagic manifestations in the first week after birth, and most develop thrombocytopenia by 4 months of age. In contrast to infants with FA, in patients with TAR syndrome both thumbs are present. The prognosis in the TAR syndrome is dependent on the severity of the hemorrhagic manifestations. If the patient survives the first year after birth, the hemorrhagic manifestations resolve, because the platelet count spontaneously improves to low normal levels which are then maintained. Treatment is supportive with platelet transfusions indicated only in the event of active bleeding.

Congenital Amegakaryocytic Thrombocytopenia

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare recessive autosomal disorder presenting during the neonatal period with thrombocytopenia. Most affected infants have petechiae or other evidence of

bleeding. Physical anomalies are present in approximately 50% of the patients. CAMT typically presents with isolated thrombocytopenia; however, 50% of the patients will later progress to aplastic anemia during infancy or early childhood. The bone marrow shows decreased to absent megakaryocytes with normal erythroid and myeloid precursors. Bleeding episodes in neonates with CAMT are treated by platelets transfusions, but stem cell transplantation is the definitive form of therapy for this disorder. There is another variant of amegakaryocytic thrombocytopenia with radioulnar synostosis. Patients with amegakaryocytic thrombocytopenia with radioulnar synostosis have a mutation in the HOXA11 gene that distinguishes them from TAR syndrome, and from CAMT in which the mutation is located in the cMPL gene.

Giant Platelet Syndromes

Giant platelet syndromes may present in the neonatal period. The characteristic of these disorders is not only a reduced platelet count, but the appearance of large platelets on the peripheral smear. Several of the rare giant platelet syndromes present in the fetus, including the May-Hegglin anomaly, which is characterized by the presence of leukocyte Dohle-like inclusion bodies. This could be a rare cause of fetal or neonatal ICH. The defect in May-Hegglin anomaly is in the MY-H9 gene on chromosome 22q. This mutation is also found in other giant platelet syndromes such as Fletcher syndrome, where leukocyte inclusions are absent and there is association of sensorial hearing loss, nephritis and cataracts, and Epstein syndrome, in which there are no leukocyte inclusions but there is association to hearing loss and nephritis without cataracts. Other macrothrombocytopenias are a group of heterogeneous disorders that include functional platelet disorders like Bernard-Soulier syndrome that was previously described, gray platelet syndrome in which there is lack of platelet granules, and Jacobsen-Paris-Trousseau syndrome that is associated with psychiatric problems or mental retardation.

Consumptive Causes of Thrombocytopenia in the Neonatal Period

Kasabach–Merritt Phenomenon

This is an important cause of thrombocytopenia in the newborn. It typically presents with profound thrombocytopenia, microangiopathic anemia, and DIC in association with a vascular malformation. The diagnosis is obvious when the vascular anomaly is cutaneous, but it may be more challenging with the presence of vascular anomalies with visceral involvement. The thrombocytopenia is due to the trapping and consumption of platelets in the endothelium of the abnormal blood vessels. The treatment of these lesions requires supportive treatment with plasma and platelet transfusion if DIC is present. Some of these vascular malformations with aggressive behavior may need treatment with steroids, interferon, vincristine, and other chemotherapy agents. More recently, the use of the angiogenesis inhibitor bevacizumab and the use of the mTOR inhibitor, rapamycin, have shown some activity; however, further studies are necessary before recommending therapy with these agents.

Thrombotic Disorders

Acquired thrombotic events in the NICU have increased over the past several years, mainly because of the high complexity of the patients cared for in the NICU requiring indwelling catheters and being at risk for several factors that predispose them to secondary thrombotic events. The use of heparin flushes to maintain the patency of indwelling catheters is also a risk for the development of heparin-induced thrombocytopenia that is associated with arterial thrombosis. Inherited deficiency of ADAMTS13, the cleaving protease of von Willebrand factor, that causes thrombotic thrombocytopenic purpura may present in the newborn period. Renal vein thrombosis should also be considered in the differential diagnosis of patients with thrombocytopenia and renal failure. Thrombocytopenia is part of the clinical presentation of anticoagulant factor deficiencies, and these deficiencies should be considered in the differential diagnosis of thrombocytopenia. However, the severe form of these deficiencies presents with purpura fulminans and diffuse thromboses and not just isolated thrombocytopenia.

Conclusions

Thrombocytopenia is a common problem in the newborn. The differential diagnosis of thrombocytopenia in the neonate can be simplified when taking into account the severity of the thrombocytopenia and the clinical appearance of the neonate. Most episodes of thrombocytopenia in the newborn occur after the first 72 hours after birth and are most commonly caused by infectious process. Persistent thrombocytopenia, or thrombocytopenia that does not respond to adequate treatment of the presumed etiology of the low platelet count, deserves further investigation to look for some of the rare causes of thrombocytopenia in neonates

including immune-related disorders, inherited thrombocytopathies and other acquired causes of platelet consumption.

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 Reading

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NeoReviews Quiz

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit*™. In order to successfully complete 2013 *NeoReviews* articles for *AMA PRA Category 1 Credit*™, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

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1. Which of the following distinguishes thrombopoiesis in neonates from adults?
   a. Megakaryocytes in neonates are larger than those found in adults.
   b. The mechanisms of neonatal response and physiology of thrombocytopenia are essentially identical to adults.
   c. The number of megakaryocyte progenitors circulating in peripheral blood of neonates is lower than in adults.
   d. Thrombopoietin does not stimulate thrombopoiesis in neonates.
   e. Thrombopoietin levels are not as high in thrombocytopenic neonates, particularly small for gestational age infants, compared with adults.

2. The laboratory calls you regarding a patient in the NICU to note an abnormal platelet count of 105,000/μL. This patient is a 2-day-old 33-weeks'-gestational-age female. Which of the following is the most appropriate management decision?
   a. A platelet level and antibody tests should be ordered for the mother.
   b. A platelet transfusion of 10 mL/kg should be given.
   c. The patient can be monitored clinically, and a platelet count can be repeated the next morning.
   d. This patient is at high risk of bleeding, particularly intracranial hemorrhage.
   e. The patient should undergo metabolic and genetic screening, including chromosomal disorders.

3. A 38-weeks'-gestational-age newborn male has a complete blood count drawn several hours after birth because of being small for gestational age, and thrombocytopenia is noted, with other parameters of the blood count being in normal ranges. In regard to the possibility of sepsis, which of the following factors would lead you to consider close observation and not giving antibiotics at this time?
   a. The platelet count is 25,000/μL, and the patient has no evidence of bleeding.
   b. The platelet count is 95,000/μL, and the patient has hypotension and capillary refill greater than 3 seconds.
   c. The platelet count is 85,000/μL, and the patient's mother has a known history of placental insufficiency.
   d. The platelet count is 50,000/μL, the patient has no bleeding symptoms but has respiratory distress requiring oxygen.
   e. Platelet count should not be considered in the evaluation for sepsis.

4. A 38-weeks'-gestational-age male presents in the well infant nursery at 2 days after delivery with mucocutaneous bleeding, and a complete blood count reveals platelet count of 25,000/μL. He appears well otherwise. He is admitted to the NICU and a cranial ultrasound reveals bilateral grade I intraventricular hemorrhage. His mother's platelet count is 175,000/μL. What is the most likely diagnosis?
   a. Bernard-Soulier syndrome.
   b. Laboratory error.
   c. Neonatal alloimmune thrombocytopenia.
   d. Neonatal autoimmune thrombocytopenia.
   e. Wiskott-Aldrich syndrome.

5. A 1-kg, 29-weeks'-gestational-age female is now 2 weeks old. She is on nasal cannula oxygen and parental nutrition via a peripherally inserted central line, and she is receiving gavage feedings of both maternal breast milk and premature infant formula. There have been increased apnea and bradycardia events over the past 24 hours with an increased need for oxygen concentration. A complete blood count reveals hematocrit of 26%, white blood cell count of 6,000/μL, and platelet count of 65,000/μL. The platelet count 1 day after delivery was noted to be 125,000/μL. What is the most appropriate next step in management of this patient?
   a. Avoid giving any medications for the next 48 hours in case thrombocytopenia may be drug-related.
   b. Give 10 mL of packed platelet transfusion over the next hour.
   c. Obtain platelet counts from the mother and father.
   d. Perform sepsis evaluation and start antibiotics while awaiting cultures.
   e. Stop giving maternal breast milk for 48 hours in case there may be passage of maternal drugs via breast milk, and instead use formula only.