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Thrombocytopenia in the Neonatal Intensive Care Unit

Matthew A. Saxonhouse, MD,* Martha C. Sola-Visner, MD†

Author Disclosure
Drs Saxonhouse and Sola-Visner 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.

Abstract
As the survival of neonates cared for in the neonatal intensive care unit (NICU) has improved, hematologic issues have been recognized as clinically significant problems in this population. Thrombocytopenia, in particular, is a common finding among sick neonates, but there is considerable debate regarding the appropriate evaluation and management of affected infants. This article provides state-of-the-art information on the pathophysiology, diagnosis, and treatment of neonatal thrombocytopenia. Specifically, the risks associated with low platelet counts in neonates are discussed, and a practical approach to the differential diagnosis of neonates who develop thrombocytopenia is provided. Current recommendations for the management of immune and nonimmune varieties of thrombocytopenia also are reviewed, with an emphasis on the risks and benefits associated with platelet transfusions in this age group.

Classification and Incidence of Neonatal Thrombocytopenia
Traditionally, thrombocytopenia in neonates (as in adults) has been defined as a platelet count of less than $150 \times 10^3$/mcL ($150 \times 10^9$/L) (1) and has been classified further as mild ($100$ to $150 \times 10^3$/mcL [$100$ to $150 \times 10^9$/L]), moderate ($50$ to $99 \times 10^3$/mcL [$50$ to $99 \times 10^9$/L]), and severe ($<50 \times 10^3$/mcL [$50 \times 10^9$/L]). Recently, the definition of neonatal thrombocytopenia was challenged by the results of a large population study involving 47,291 neonates from a large multihospital system. In this study, the lower 5th percentiles for platelet counts were $104.2 \times 10^3$/mcL ($104.2 \times 10^9$/L) and $123.1 \times 10^3$/mcL ($123.1 \times 10^9$/L) for infants younger than 32 weeks’ gestation and late preterm/term neonates, respectively. (2) Because this study did not exclude ill neonates, however, these values should be

Abbreviations
CMV: cytomegalovirus
ELBW: extremely low birthweight
GA: gestational age
GVHD: graft versus host disease
HPA: human platelet antigen
MPV: mean platelet volume
IPF: immature platelet fraction
ITP: immune thrombocytopenic purpura
IVIG: intravenous immune globulin
NAIT: neonatal alloimmune thrombocytopenia
NICU: neonatal intensive care unit
RP%: reticulated platelet percentages
Tpo: thrombopoietin
vWF: von Willebrand

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interpreted as epidemiologic “reference values” for neonates admitted to the NICU rather than as “normal values” for this population.

Applying the original definition of neonatal thrombocytopenia (ie, a platelet count $<150 \times 10^3$/mcL [150 $\times 10^9$/L]), several studies have shown that 18% to 35% of all neonates admitted to the NICU develop thrombocytopenia at some point during their NICU stays. (3)(4) The incidence of thrombocytopenia seems to be inversely related to gestational age (GA), with the highest numbers found among the most immature infants. In a recent cohort analysis, Christensen and associates (4) observed that 73% of extremely low-birthweight (ELBW) infants had one or more recorded platelet counts below $150 \times 10^3$/mcL (150 $\times 10^9$/L), most frequently during the first postnatal week. Furthermore, within that group, thrombocytopenia occurred in 85% of neonates who weighed less than 800 g at birth and in 60% whose birthweights were between 801 and 900 g.

When interpreting a low platelet count in the NICU, it is important to recognize that improper collection techniques or unrecognized platelet clumping can produce a falsely low value. This is particularly important in a well-appearing neonate who has no risk factors for thrombocytopenia and no signs of thrombocytopenia on clinical examination. In these cases, the low platelet count should be confirmed by repeat sampling.

**Neonatal Platelet Function and Risks of Thrombocytopenia**

Multiple in vitro studies measuring platelet function in cord blood samples (by platelet aggregometry and flow cytometry) have shown consistently that neonatal platelets (preterm > term) are hyporesponsive to most platelet agonists compared with platelets from adults. (5)(6) Paradoxically, however, results of whole blood assays of primary hemostasis (such as the bleeding time or platelet function analysis) performed on term neonates or on term cord blood samples suggested slightly enhanced hemostasis in neonates compared with adults. (7)(8) Similarly, whole blood coagulation assays such as thromboelastography revealed that neonatal coagulation times were equal to or shorter than those from adults, again suggesting adequate hemostasis. (9) Although the exact causes for these findings are not completely understood, it has been theorized that the higher hematocrits, higher mean corpuscular volumes, higher von Willebrand factor (vWF) values, and presence of ultra-large vWF polymers in neonates account for the disparities between the results of pure platelet function assays and tests of global hemostasis. (10)(11)

Most of these studies focused exclusively on term infants, but a number of recent reports have evaluated the effects of GA and postconceptional age (GA + postnatal weeks) on platelet function. Briefly, these studies demonstrated that: 1) platelet response to agonists and platelet procoagulant activity were significantly decreased in ELBW infants during the first days after birth compared with adults, but improved by postnatal days 10 to 14; (12) 2) bleeding times assessed on postnatal day 1 in infants born at 24 to 33 weeks’ gestation were twice as high as those in infants born at 38 to 41 weeks’ gestation, but also improved by postnatal day 10; (13) and 3) CT-ADP closure times (an in vitro measure of primary hemostasis) were inversely related to GA in both cord blood and peripheral blood samples obtained on postnatal days 1 to 2. (14) Although these observations strongly support the existence of developmental deficiencies in primary hemostasis in preterm neonates during the first 1 to 2 weeks after birth, the question of whether (and to what degree) such hemostatic abnormalities contribute to the pathophysiology of intraventricular hemorrhage remains unanswered. Nevertheless, important factors must be considered when deciding the point at which the bleeding risk for a neonate who has thrombocytopenia justifies intervention (ie, with platelet transfusions).

**Approach to the Neonate Who Has Thrombocytopenia**

One of the most helpful pieces of information when evaluating a neonate exhibiting thrombocytopenia is the time of presentation. Although there is some overlap, the pathologic processes that cause thrombocytopenia at birth or during the first 72 hours after birth generally differ from those accounting for thrombocytopenia presenting after 72 hours. We, therefore, classify the causes of thrombocytopenia into early-onset and late-onset (Tables 1 and 2).

**Early-onset Thrombocytopenia**

The initial evaluation for neonates who have early-onset thrombocytopenia is based on the severity of thrombocytopenia, the clinical presentation (Table 1), and the maternal history. The latter is particularly important if the mother has autoimmune thrombocytopenia. If that is the case, the most likely diagnosis in an otherwise well-appearing neonate is autoimmune thrombocytopenia, mediated by the transplacental passage of maternal autoantibodies. Other important clues in the maternal history
are preeclampsia or chronic hypertension, which are frequent causes of placental insufficiency. This is the most common cause of mild thrombocytopenia in healthy-appearing neonates (particularly those born preterm) and can be managed expectantly with close observation. (15) This type of thrombocytopenia is always mild-to-moderate, reaches a nadir on postnatal days 4 to 5, and invariably resolves by 7 to 10 days after birth. Thus, either progression to severe thrombocytopenia or lack of resolution within this timeframe should prompt evaluation for other causes. The clinical condition of affected infants should be monitored closely because thrombocytopenia can be the first presenting sign of a serious condition (eg, sepsis). For this reason, many clinicians order blood cultures and consider administering antibiotics for well-appearing neonates in whom the cause of the thrombocytopenia is not yet clearly defined.

The presence of early-onset thrombocytopenia (of any severity) in an ill-appearing term or preterm neonate should trigger suspicion for bacterial or viral sepsis, TORCH (Toxoplasma, rubella, cytomegalovirus [CMV], herpes simplex virus) infections, or disseminated intravascular coagulation (eg, related to perinatal asphyxia). The physical examination can provide important clues to the diagnosis, such as hepatosplenomegaly in congenital viral infections. Appropriate tests should be ordered, and treatment should be initiated based on index of suspicion.

Early-onset severe thrombocytopenia in a well-appearing neonate is primarily suggestive of immune thrombocytopenia, caused by the passage of antiplatelet antibodies from the mother to the fetus. In the absence of maternal thrombocytopenia, the most likely diagnosis is neonatal alloimmune thrombocytopenia (NAIT). However, if a careful physical examination reveals congenital anomalies or dysmorphic features, a number of genetic disorders known to be associated with thrombocytopenia also should be considered and evaluated (Table 3). In these cases, the platelet size, represented by mean platelet volume (MPV), and a review of the peripheral blood smear can assist in narrowing the differential diagnosis. For example, Jacobsen syndrome and Fechtner syndrome present with large platelets and other associated clinical findings, (16) and Wiskott-Aldrich syndrome and X-linked thrombocytopenia present with small platelets (MPV typically <7 fL). Certain entities, such as congenital amegakaryocytic thrombocytopenia (mutations in the receptor for thrombopoietin without other congenital anomalies), can be almost indistinguishable from NAIT in the neonatal period. Response to treatments (or lack thereof), long survival of transfused platelets, and persistence of the thrombocytopenia beyond the neonatal period are clues to the correct diagnosis.

### Late-onset Thrombocytopenia

The evaluation of neonates who have late-onset thrombocytopenia (Table 2) also is based on the severity of

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**Table 1. Differential Diagnosis of Neonatal Early-onset* Thrombocytopenia**

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Degree of Thrombocytopenia</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ill-appearing</td>
<td>Variable</td>
<td>Sepsis (bacterial, viral†) TORCH‡ infections Birth asphyxia</td>
</tr>
<tr>
<td>Well-appearing</td>
<td>Mild-to-moderate</td>
<td>Placental insufficiency Genetic disorders (see Table 3) Autoimmune Neonatal alloimmune thrombocytopenia Genetic disorders (see Table 3) Autoimmune</td>
</tr>
</tbody>
</table>

*≤72 hours after birth
†Causative viruses: cytomegalovirus, human immunodeficiency virus, herpes simplex virus, enteroviruses
‡Toxoplasma, rubella, cytomegalovirus, herpes simplex virus

**Table 2. Differential Diagnosis of Neonatal Late-onset* Thrombocytopenia†**

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ill-appearing</td>
<td>Sepsis (bacterial, viral*, fungal) Necrotizing enterocolitis Inborn error of metabolism</td>
</tr>
<tr>
<td>Well-appearing</td>
<td>Drug-induced thrombocytopenia Thrombosis Fanconi anemia</td>
</tr>
</tbody>
</table>

*≥72 hours after birth
†Due to clinical variability in presentations, differential diagnosis applies to all degrees of thrombocytopenia.
‡Causative viruses: herpes simplex virus, cytomegalovirus, enteroviruses
thrombocytopenia and the clinical condition of the infant. In general, late-onset thrombocytopenia should prompt rapid evaluation and treatment for bacterial/fungal sepsis; viral infections such as herpes simplex virus, acquired cytomegalovirus, or enteroviruses; and necrotizing enterocolitis (Table 2). If these most common causes are ruled out, other potential causes include inborn errors of metabolism (eg, propionic acidemia, isovaleric acidemia, methylmalonic acidemia, and Gaucher disease), thromboses (eg, renal vein thrombosis), or drug-induced thrombocytopenias (eg, heparin, antibiotics). Fanconi anemia is a bone marrow failure syndrome
that rarely presents with cytopenia in the neonatal period, although cases have been described. (17)

Mechanisms of Nonimmune Thrombocytopenia

Neonatal Platelet Production

Platelet production in neonates, as in adults, can be represented schematically as consisting of four primary steps: 1) production of thrombopoietin (Tpo), the most potent stimulator of platelet production; 2) proliferation of megakaryocyte progenitors (the cells that multiply and give rise to megakaryocytes); 3) megakaryocyte maturation; and 4) generation and release of new platelets. (18) However, significant developmental differences exist between neonates and adults in regard to platelet production. Specifically, plasma Tpo concentrations are higher in healthy neonates than in healthy adults, (19)(20) whereas neonates who have thrombocytopenia generally have lower Tpo concentrations than similarly affected adults. (19)(21) Neonatal megakaryocyte progenitors have a higher proliferative potential than adult progenitors, (22) but neonatal megakaryocytes are smaller and of lower ploidy than adult megakaryocytes (and, therefore, generate fewer platelets per megakaryocyte). Thus, it has been postulated that under normal conditions, neonates maintain their platelet counts on the basis of the increased proliferative potential of their progenitors. (23) In response to thrombocytopenia, however, recent studies have shown that neonates can increase the number, but not the size, of their megakaryocytes, (24) a developmental limitation that might aid in explaining the predisposition of ill neonates to develop thrombocytopenia.

Measurements of Neonatal Platelet Production

In adults, bone marrow biopsy is the gold-standard test for the mechanistic evaluation of thrombocytopenia. In neonates, however, this procedure can be technically difficult and frequently is postponed until the infant is out of the neonatal period. With the hope of overcoming this limitation, a number of potentially useful indirect measurements of platelet production were developed over the past decade, including plasma or serum Tpo concentrations, (25) circulating megakaryocyte progenitors, (26) reticulated platelet percentages (RP%), (27) and glycoplasticin concentrations. (28) To date, most of these tests are only available in the research setting. However, a test similar to the RP% recently was developed for clinical use. This RP% equivalent, termed the “immature platelet fraction (IPF),” can be measured by a standard hematology analyzer as part of a routine complete blood count. Similarly to the RP% (and to the reticulocyte count in the evaluation of anemia), IPF values are elevated in thrombocytopenic conditions associated with increased platelet destruction (eg, immune thrombocytopenic purpura [ITP]) and decreased in thrombocytopenias due to decreased platelet production (eg, aplastic anemia, chemotherapy-induced thrombocytopenia). (29)(30) Only one study has evaluated IPF values in neonates who do not have thrombocytopenia and in neonates who have early-onset thrombocytopenia. This single study reported that normal neonatal IPF values were higher than those previously reported in adults, likely reflecting an increased amount of platelet production in neonates (necessary to maintain a normal platelet count during a period of rapid growth). (31) Most importantly, however, findings from this study suggested that the IPF could be used (at least in certain varieties of thrombocytopenia) to predict recovery of the platelet count within the next 24 hours. Thus, the IPF has the potential of becoming an important new tool in the evaluation and management of neonatal thrombocytopenia.

Mechanisms of Thrombocytopenia in Specific Neonatal Illnesses

Although none of the indirect measurements has yet been validated adequately with concomitant bone marrow or platelet kinetic studies in neonates, reports in adults and children suggest that the use of several tests in combination can help differentiate between disorders of increased platelet destruction and those of decreased production. (28)(32)(33)(34) Indeed, the use of such markers of thrombopoiesis already has provided significant insight into the mechanisms of some common varieties of neonatal thrombocytopenia, particularly those associated with chronic intrauterine hypoxia/placental insufficiency and sepsis.

Several studies have implicated platelet underproduction as the primary mechanism for the thrombocytopenia frequently seen in fetuses and neonates exposed to chronic intrauterine hypoxia. (15)(19) Decreased concentrations of circulating megakaryocyte progenitors and decreased numbers of megakaryocytes in the bone marrow of preterm neonates who have such thrombocytopenia have been described and have been associated with lower-than-expected plasma Tpo concentrations. In vitro studies also have suggested that the hematopoietic microenvironment plays a significant role in mediating chronic hypoxia-induced suppression of megakaryocytopoiesis and that megakaryocyte progenitors from pre-
term neonates are more vulnerable than progenitors from term neonates or adults. (35)

Several studies have focused on the pathogenesis of thrombocytopenia in sepsis and have described elevated Tpo concentrations in septic neonates. A recent evaluation of 20 neonates who had sepsis or necrotizing enterocolitis showed that Tpo and circulating megakaryocyte progenitor concentrations as well as the RP% were elevated. (36) Taken together, these findings suggested an upregulation of thrombopoiesis mediated by Tpo. Surprisingly, however, the degree of upregulation was rather modest (two- to threefold), and the neonates who had gram-negative sepsis did not exhibit the most significant increases in thrombopoiesis, despite having more severe thrombocytopenia and more severe illness. This suggested that the thrombopoietic response in neonates can be downregulated during severe illness and can reach a state of “relative hypoproliferation.” (37)

Management of Neonatal Thrombocytopenia

Neonatal Alloimmune Thrombocytopenia (NAIT)

NAIT should be considered in any neonate who has an initial platelet count of less than $5 \times 10^3$/mL ($50 \times 10^9$/L), especially in the absence of other risk factors or clinical symptoms. A study of more than 150 neonates who had thrombocytopenia found that when a platelet count of less than $5 \times 10^3$/mL ($50 \times 10^9$/L) was used as a screen, 90% of the patients who had NAIT were identified. (38) In addition, the combination of severe neonatal thrombocytopenia with a parenchymal (rather than intraventricular) intracranial hemorrhage is highly suggestive of NAIT. When NAIT is suspected, rapid blood testing is very important for timely and accurate diagnosis. Blood should be collected from the mother and father and submitted for confirmatory testing (if easily accessible). Antigen screening, based on current recommendations, initially should include human platelet antigen (HPA) 1, 3, and 5. (39) This evaluation should identify approximately 90% of cases of NAIT. However, if the diagnosis is strongly suspected and the initial evaluation results are negative, further testing should be undertaken for HPA 9 and 15 (and HPA 4 if the parents are of Asian descent). (39) Evaluation, if results are positive, reveals an antibody in the mother’s plasma directed against the specific platelet antigen in the father. If blood cannot be collected from the parents in a timely fashion, the neonate’s serum can be screened for platelet antibodies. However, a low antibody concentration in the neonate coupled with binding of the antibodies to the neonate’s platelets may result in a false-negative result.

Due to the complexity of testing, evaluations should be performed in a very experienced reference laboratory that has a large number of typed controls available for antibody detection and the appropriate DNA-based technology to type multiple antigens. (39) Imaging of the brain (ultrasonography, computed tomography scan, or magnetic resonance imaging) is mandatory and should be performed as soon as possible when a diagnosis of NAIT is suspected. Findings from these studies dictate the aggressiveness of the treatment regimen in the neonate as well as in the mother’s future pregnancies.

Based on recent data demonstrating that a large proportion of infants who have NAIT respond to random donor platelet transfusions just as well as neonates who have nonimmune thrombocytopenia, random donor platelet transfusions now are considered the first line of therapy for infants in whom NAIT is suspected. (40) If the patient is clinically stable and does not have evidence of an intracranial hemorrhage, we recommend transfusing platelets if the platelet count is less than $30 \times 10^3$/mL ($30 \times 10^9$/L). If the patient has evidence of an intracranial hemorrhage, the goal is to maintain a platelet count greater than $100 \times 10^3$/mL ($100 \times 10^9$/L). In addition to platelets, if a diagnosis of NAIT is confirmed or suspected, intravenous immune globulin (IVIG) (1 g/kg for up to 2 consecutive days) can be infused to increase the patient’s own platelets and potentially to protect the transfused platelets when they are administered. (41) If these treatment options do not efficiently increase the platelet count to a safe concentration within 1 to 2 days, matched (antigen-negative) platelets must be provided. Several versions of matched platelets exist, including: 1) maternal platelets, which need to be concentrated prior to transfusion to limit the amount of serum transfused to the baby; 2) donor platelets, which are matched after obtaining the results of typing. (39) In addition, methylprednisolone (1 mg/kg intravenously every 8 hours) might be used on the days that IVIG is being administered. (39) The clinical course of NAIT is short in most cases, often resolving almost entirely within 2 weeks. However, to confirm the diagnosis, it is important to follow the platelet count frequently until a normal count is achieved off treatment.
Autoimmune Thrombocytopenia
The diagnosis of neonatal autoimmune thrombocytopenia should be considered in any neonate who has early-onset moderate-to-severe thrombocytopenia and a maternal history of either ITP or an autoimmune disease with or without thrombocytopenia. A recent retrospective study of obstetric patients who had ITP (including a high number of mothers who had thrombocytopenia during their pregnancies) demonstrated a high incidence of affected babies, with 25% of neonates exhibiting thrombocytopenia at birth, 9% having severe thrombocytopenia, and 15% receiving treatment for the thrombocytopenia. (43) Based on this review, it is recommended that all neonates born to mothers who have autoimmune diseases undergo a screening platelet count shortly after birth. If the platelet count is normal, no further evaluation is necessary. (44) If the neonate has mild-to-moderate thrombocytopenia, the platelet count should be repeated in 2 to 3 days. If the platelet count is less than $30 \times 10^9$/mL ($30 \times 10^9/L$), IVIG (1 g/kg for up to 2 consecutive days) is the first line of therapy. (45) Random donor platelets, in addition to IVIG, should be provided if the infant has evidence of active bleeding. Cranial imaging should be used to evaluate for intracranial hemorrhage.

Nonimmune Thrombocytopenia
The management of neonatal nonimmune thrombocytopenia consists primarily of determining the cause and providing diagnosis-specific therapy and supportive care. For patients who have moderate-to-severe thrombocytopenia, the mainstay of therapy is platelet transfusion, which is indicated at different thresholds, depending on the patient’s clinical status and whether there are any signs of hemorrhage.

Platelet Transfusions in the NICU
Recent surveys, in concordance with prior studies, have revealed substantial variability in platelet transfusion thresholds among neonatologists worldwide. (46)(47) Although the causes for such diversity are multifactorial, the lack of solid evidence to guide neonatal platelet transfusion decisions is likely a major contributing factor. To date, only one prospective, randomized trial has compared different platelet transfusion thresholds in neonates. This study, which was limited to very low-birthweight infants during the first postnatal week, (48) found no differences in the incidence or severity of intraventricular hemorrhages when platelet transfusions were administered for platelet counts less than $150 \times 10^9$/mcL ($100 \times 10^9/L$) versus less than $50 \times 10^9$/mcL ($50 \times 10^9/L$). One additional retrospective study addressed the question of whether platelet counts of less than $50 \times 10^9$/mcL ($50 \times 10^9/L$) could be tolerated safely in the NICU. (49) The investigators concluded that using a platelet count of $30 \times 10^9$/mcL ($30 \times 10^9/L$) as a transfusion threshold was a safe practice for clinically stable neonates, particularly after the first postnatal week. (49)

Based on this very limited evidence, we currently recommend transfusing platelets to preterm neonates (<33 weeks gestational age) and to clinically unstable term infants during the first postnatal week for platelet counts below $50 \times 10^9$/mcL ($50 \times 10^9/L$). After the first postnatal week, the threshold can be lowered to $30 \times 10^9$/mcL ($30 \times 10^9/L$) in clinically stable infants.

Platelet transfusions should be given for platelet counts less than $100 \times 10^9$/mcL ($100 \times 10^9/L$) to neonates who have signs of active bleeding. (44)

More consensus has been reached regarding which blood products to use. Most experts agree that neonates should receive 10 to 15 mL/kg of a standard platelet suspension, such as platelet concentrates (random-donor platelets) or apheresis platelets. Whole blood-derived platelet concentrates (random-donor platelets) are obtained from a single donated unit of whole blood. Each random-donor platelet unit has approximately 50 mL of volume and contains approximately $10 \times 10^9$ platelets per 10 mL. (50) A single random-donor platelet unit usually is sufficient to provide a platelet transfusion to a neonate weighing 5 kg or less and should raise the platelet count to more than $100 \times 10^9$/mcL ($100 \times 10^9/L$). (51) There is no need to pool more than one random-donor unit for a neonatal transfusion, a practice that (while still somewhat prevalent) only increases donor exposures without any benefit. Apheresis platelets are collected via an apheresis machine that removes platelets from the donor while returning the remaining constituents of whole blood. Each apheresis platelet unit contains five to eight large units. (52)

Two additional important considerations in neonatology are the prevention of transfusion-transmitted CMV infections and graft versus host disease (GVHD). It is widely accepted that neonates should receive only CMV-safe blood products. Which product is safest remains controversial, but most blood banks provide CMV-negative or leukoreduced products to neonates, which reduces (but does not eliminate) the risk of transfusion-transmitted CMV infection. GVHD is effectively pre-
vented by irradiating cellular blood products prior to transfusing neonates. This practice is absolutely indicated for neonates who have suspected or confirmed immunodeficiency as well as neonates receiving intrauterine or exchange transfusions, human leukocyte antigen-matched blood, or blood from a first- or second-degree relative. (51)(53) However, because a primary immunodeficiency might not yet have been recognized in the neonatal period, many blood banks choose to provide irradiated blood products to all neonates.

It is important for neonatologists to be aware of the risks associated with platelet transfusions for neonates. Specifically, platelet transfusions have been associated with transfusion-associated lung injury, a process characterized by the onset of hypoxemia and bilateral pulmonary infiltrates within 6 hours of a transfusion, which is likely underrecognized and underreported in the NICU. (54) From the infectious standpoint, the primary concern with platelet transfusions is the risk of bacterial contamination, which is higher than the combined risk of all viral infections for which platelets routinely are tested. (55) Several recent publications have shown a strong association between the number of platelet transfusions and the mortality rate among NICU patients. (56)(57) It is unclear from these studies whether this association simply reflects sicker patients receiving more platelets or platelet transfusions adversely affecting outcome. Nevertheless, platelet transfusion decisions in neonates should be made thoughtfully, carefully balancing the risks and benefits in each individual patient. It is also clear that well-designed randomized, controlled studies are needed to provide solid evidence on which to base transfusion decisions.

**Thrombopoietic Growth Factors**

Because of the risks associated with the use of blood products, thrombopoietic growth factors have been investigated as potential therapies for thrombocytopenia. Three thrombopoietic agents are currently available for clinical use. Recombinant interleukin-11 was the first factor approved by the United States Food and Drug Administration for the prevention of severe chemotherapy-induced thrombocytopenia. However, significant adverse effects, such as fluid retention and atrial arrhythmias, somewhat limited its use. (58)

In 2008, two novel thrombopoietic agents were approved for the treatment of chronic refractory ITP: romiplostim and eltrombopag. Both are thrombopoietin-mimetics, implying that they have no homology with thrombopoietin but act by binding to the thrombopoietin receptor on megakaryocytes, thus displaying very similar effects to thrombopoietin. Both compounds have demonstrated high efficacy and a favorable safety profile in adults who have thrombocytopenia. However, their safety and efficacy have not been evaluated in neonates. Based on recent data suggesting that thrombopoietin has different effects on neonatal compared with adult megakaryocytes, (59) it seems judicious at this point to pursue additional preclinical research on the effects of these compounds on neonatal organisms and to limit their clinical use in neonates to well-designed clinical trials. Furthermore, 4 to 6 days are required for the platelet count to start rising after therapy with thrombopoietic agents. Because the median duration of thrombocytopenic episodes in neonates is 7 days, the use of thrombopoietic factors appears justified only in carefully selected neonates who have varieties of thrombocytopenia that are expected to be more prolonged.

**Conclusion**

Thrombocytopenia is a common problem in the NICU, particularly among preterm infants. Most cases are mild to moderate and do not warrant aggressive treatment. However, approximately 6% of all infants admitted to the NICU develop severe thrombocytopenia, defined as a platelet count less than $50 \times 10^9$/mcL ($50 \times 10^9$/L). A thorough and stepwise approach to the neonate who has thrombocytopenia usually leads to the correct diagnosis, allows appropriate treatment, and minimizes complications. However, there is little consensus on when to administer platelet transfusions to avoid significant hemorrhage, and current recommendations are based on very limited scientific evidence. Large, well-designed, randomized, controlled trials are needed to address this question.

**American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications**

- Know the causes and pathophysiology of neonatal thrombocytopenia and thrombocytosis.
- Know the clinical and laboratory manifestations and management of neonatal thrombocytopenia and thrombocytosis.

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**NeoReviews Quiz**

1. Thrombocytopenia is defined as a platelet count less than $150 \times 10^3/\text{mL}$ ($150 \times 10^3/\text{L}$) in neonates, as in adults. Using this definition, the incidence of thrombocytopenia among infants admitted to a neonatal intensive care unit has been shown to vary inversely with the gestational age of the infant. Of the following, the estimated incidence of thrombocytopenia among infants whose birthweights are less than 800 g, as reported by Christensen and associates, is closest to:

A. 25%.
B. 40%.
C. 55%.
D. 70%.
E. 85%.

2. Thrombocytopenia is classified based on the platelet count as mild (100 to $150 \times 10^3/\text{mL}$ [100 to $150 \times 10^3/\text{L}$]), moderate (50 to $99 \times 10^3/\text{mL}$ [50 to $99 \times 10^3/\text{L}$]), or severe ($<50 \times 10^3/\text{mL}$ [50 to $10^3/\text{L}$]). It is also classified as early-onset (onset within 72 hours after birth) or late-onset (onset more than 72 hours after birth). This classification is helpful in identifying the cause of thrombocytopenia in neonates. Of the following, the most common cause of mild, early-onset thrombocytopenia in a well-appearing neonate is:

A. Alloimmune disease.
B. Birth asphyxia.
C. Genetic disorder.
D. Placental insufficiency.
E. Viral/fungal sepsis.
3. Evaluation of a neonate who has late-onset thrombocytopenia is based on the severity of thrombocytopenia and the clinical condition of the infant. Of the following, the most common cause of severe, late-onset thrombocytopenia in an ill-appearing neonate is:

A. Bacterial/viral sepsis.
B. Drug-induced thrombocytopenia.
C. Fanconi anemia.
D. Inborn error of metabolism.
E. Venous thrombosis.

4. Platelet production in neonates, as in adults, occurs in four primary steps: production of thrombopoietin, proliferation of megakaryocyte progenitors, maturation of megakaryocytes, and generation and release of new platelets. Several tests have been designed to determine whether thrombocytopenia is caused by decreased production of platelets or by increased destruction or consumption of platelets. Of the following, the test of platelet production that has the greatest potential for clinical application in the evaluation of neonatal thrombocytopenia is:

A. Bone marrow biopsy.
B. Circulating megakaryocyte progenitor count.
C. Immature platelet fraction test.
D. Serum glycolytic concentration.
E. Serum thrombopoietin concentration.

5. Neonatal alloimmune thrombocytopenia (NAIT) results from maternal immunization to a foreign fetal platelet antigen derived from the father and subsequent transplacental passage of maternally derived antibodies into the fetal circulation. Of the following, the first line of treatment for infants who have suspected NAIT is the administration of:

A. Intravenous immune globulin.
B. Methylprednisolone.
C. Random donor platelets.
D. Recombinant interleukin-11.
E. Thrombopoietin mimetic.

6. The threshold for transfusion of platelets in neonates who have thrombocytopenia varies with the infant's age and clinical stability as well as evidence of active bleeding in the infant. Of the following, the threshold for platelet transfusion in a clinically stable neonate after the first week of age, as recommended by Murray and associates, is a platelet count of less than:

A. $30 \times 10^3$/mL ($30 \times 10^9$/L).
B. $50 \times 10^3$/mL ($50 \times 10^9$/L).
C. $75 \times 10^3$/mL ($75 \times 10^9$/L).
D. $100 \times 10^3$/mL ($100 \times 10^9$/L).
E. $150 \times 10^3$/mL ($150 \times 10^9$/mL).
Thrombocytopenia in the Neonatal Intensive Care Unit
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