

**Bleeding Disorders in the Neonate**

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# Bleeding Disorders in the Neonate

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Dr Manco-Johnson did not disclose any financial relationships relevant to this article.

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

1. Recognize the most common bleeding syndromes in otherwise well newborns.
2. Recognize the most common bleeding syndromes in sick term and preterm newborns.
3. Interpret coagulation screening tests to diagnose the most likely cause(s) of bleeding in symptomatic newborns.
4. Understand the range of therapies for treating bleeding disorders.

## Abstract

Bleeding syndromes in the newborn are rare, but they may be life-threatening and demand immediate attention. Results of an initial coagulation evaluation often can direct the clinician toward diagnostic possibilities, as can the degree of illness manifested by the infant. Among the potential causes of neonatal bleeding are platelet disorders, neonatal hemophilia and other congenital clotting factor deficiencies, vitamin K deficiency syndromes, liver failure, and disseminated intravascular coagulation. Depending on the cause, platelet or protein concentrates may be used for transfusion therapy.

## Introduction

Although rare, bleeding syndromes in the newborn may be life-threatening and demand immediate attention. Two major clinical indicators can be used to establish the differential diagnosis of neonatal bleeding syndromes: 1) whether the bleeding infant is an otherwise well baby or is obviously ill, and 2) whether platelet or plasma coagulation protein deficiencies appear to be primarily involved in the coagulopathy.

Neonatal bleeding syndromes include intracranial hemorrhage (ICH) as well as subgaleal, retroperitoneal, gastrointestinal, parenchymal, or skin hemorrhage. Anemia and jaundice are common in infants who are experiencing significant internal hemorrhage. In addition, infants who have ICH can present with seizures, depressed sensorium, apnea, and weakness. Petechiae are pathognomonic of platelet-mediated bleeding; palpable hematomas are more common in deficiencies of plasma coagulation proteins.

An initial coagulation evaluation to assess neonatal bleeding should include a prothrombin time (PT), fibrinogen, D-dimer, platelet count, and indicator of platelet function, such as the platelet function analyzer-100 (PFA-100). The activated partial thromboplastin time (PTT) often is informative in the term infant, but due to the physiologic prolongation of the PTT related to prematurity, seldom adds useful information in the extremely preterm infant. An assay of fibrin degradation products (fibrin split products) may be substituted for the D-dimer assay, but requires an additional blood tube and a larger total blood volume for the evaluation. A general guide to interpretation of results of screening coagulation assays is shown in Table 1.

Platelet function can be difficult to assess in newborns. The PFA-100 closure time and template bleeding time normally are shorter in term infants than healthy children or adults and normal or only mildly increased in preterm infants. The PFA detects many, but not all, cases of significant platelet function defect or von Willebrand disease but cannot assess connective tissue for bleeding disorders such as Ehlers-Danlos syndrome. The template bleeding time assesses the infant's connective tissue directly but is not generally favored

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Table 1. Typical Patterns of Coagulation Screening Tests in Newborns

Condition	PTT	PT	Fibrinogen	D-Dimer	Platelet Count	PFA-100
Well term infant	Normal to ↑	Normal to ↑	Normal	Negative to ↑	Normal	↓
Well preterm infant	Normal to ↑↑	Normal to ↑	Normal	Negative to ↑	Normal	Normal to ↓
Hemophilia A or B	↑↑↑	Normal	Normal	Negative to ↑	Normal	Normal to ↓
Severe von Willebrand disease	↑↑	Normal	Normal	Negative to ↑	Normal	↑↑ to ↑↑↑
Thrombocytopenia	Normal to ↑	Normal	Normal	Negative to ↑	↓ to ↓↓↓	↑↑ to ↑↑↑
Platelet dysfunction	Normal to ↑	Normal	Normal	Negative to ↑	Normal to ↓	↑↑ to ↑↑↑
Heparin contamination	↑↑ to ↑↑↑	Normal to ↑↑	Normal	Negative to ↑	Normal	Normal to ↓
Vitamin K deficiency	↑ to ↑↑	↑↑ to ↑↑↑	Normal	Negative to ↑	Normal	Normal to ↓
Sepsis	↓ to ↑↑	↑ to ↑↑	Normal to ↓	↑↑ to ↑↑↑	↓↓ to ↓↓↓	↑↑ to ↑↑↑
Hypoxia	↑ to ↑↑	Normal to ↑↑	Normal to ↓	↑↑ to ↑↑↑	↓ to ↓↓	Normal to ↑↑
Liver failure	↑ to ↑↑↑	↑↑ to ↑↑↑	Normal to ↓	↑↑ to ↑↑↑	↓ to ↓↓	↑↑ to ↑↑↑
Disseminated intravascular coagulation	↑ to ↑↑↑	↑ to ↑↑↑	Normal to ↓	↑↑ to ↑↑↑	↓ to ↓↓	↑↑ to ↑↑↑

PTT=partial thromboplastin time, PT=prothrombin time, PFA=platelet function analyzer, one arrow=mild, two arrows=moderate, three arrows=severe

because of scarring from the skin incision. Standard platelet aggregation studies require 10 to 20 mL of whole blood, and the lower end of the sample range can be obtained only from a large term infant. It is possible to perform platelet aggregation assays by activating platelets in small whole blood samples and detecting platelet activation using flow cytometry for platelet receptors that are expressed only following activation. This technique can be very informative but generally is not available in clinical laboratories. All techniques to assess platelet function are inaccurate when the platelet count is less than  $100 \times 10^3/\text{mL}$  ( $100 \times 10^9/\text{L}$ ).

Obtaining blood samples adequate to perform screening coagulation studies can be a challenge in newborns, especially small preterm infants. Blood samples obtained from indwelling vascular catheters frequently are contaminated with heparin used to maintain patency in the lines. Heparinase is a chemical that can degrade unfractionated or low-molecular weight heparin. When added to a final concentration of 25 mg/mL, heparinase neutralizes up to 2 U/mL unfractionated heparin and allows accurate performance of coagulation screening tests and specific assays, although, of course, it is not useful to measure therapeutic heparin effect in plasma obtained through indwelling catheters. Carefully collected heel-stick samples that are dripped directly into centrifuge

tubes containing citrate appropriate for a premarked volume can be used to assay PT, thrombin time, fibrinogen, many factor assays, noncarboxylated prothrombin, and anti-Xa activity. Heel-stick samples cannot be used for PTT or factor VIII assay.

### Bleeding in Otherwise Well Newborns

Bleeding in otherwise well infants may be apparent in the delivery room or may present after the infant is discharged from the nursery. It is important to establish first the timing, site, and extent of bleeding. Petechiae and ecchymoses that present at or shortly following delivery most often are signs of thrombocytopenia, as is prenatally diagnosed ICH. Bleeding in an infant who has skeletal anomalies often indicates a congenital thrombocytopenia syndrome.

### Pseudohemorrhage in the Newborn

Fresh blood coming from the stomach of a newborn may be of fetal or maternal origin; swallowed maternal blood cannot be discerned by visual inspection. An Apt test of the blood, based on maintenance of pink color of fetal but not adult hemoglobin diluted in 1% sodium hydroxide, can help determine the origin of blood cells.

## Platelet Disorders Causing Neonatal Bleeding

### Neonatal Alloimmune Thrombocytopenia (NAIT)

Fetal and neonatal thrombocytopenia resulting from maternal antibodies directed against fetal antigens that the mother lacks, most often the PLA-1 antigen, develop in approximately 1 in 1,000 infants. Fifty percent of cases occur during first pregnancies, and subsequently affected infants tend to have more severe courses. Skin manifestations of bleeding are most common, but intracranial and gastrointestinal bleeding also may occur. The diagnosis is suggested by severe thrombocytopenia (platelet count  $<10 \times 10^3/\text{mCL}$  [ $10 \times 10^9/\text{L}$ ]) in an otherwise stable infant whose mother has a normal platelet count. The diagnosis of NAIT is confirmed by the determination of antibodies in maternal serum directed against platelet antigens that have a consistent paternal platelet genotype. Treatment consists of maternal platelet transfusion to the infant who is symptomatic or has an extremely low platelet count. The disorder abates rapidly following birth, and repeated platelet transfusions are not needed as a rule. Intravenous immunoglobulin (IVIg) also is helpful in increasing the platelet count following administration either to the mother at and beyond 32 weeks' gestation or postnatally to the infant. Coagulation evaluation reveals a normal PT and fibrinogen value. D-dimer may be somewhat elevated following an extensive hemorrhage or the birth process, but it is not elevated to the degree found in disseminated intravascular coagulation (DIC).

### Maternal Immune Thrombocytopenia Purpura (ITP)

Maternal ITP also can cause symptomatic thrombocytopenia in an affected fetus, although the thrombocytopenia is less frequent and less severe than that found in NAIT. Mothers who have ITP often exhibit thrombocytopenia. Postnatal steroids or IVIg can aid in increasing neonatal platelet counts in bleeding infants.

### Congenital Thrombocytopenia

Several gene mutations cause neonatal thrombocytopenia. Some congenital thrombocytopenia syndromes are associated with skeletal defects, including the thrombocytopenia with absent radius syndrome (TAR) and Fanconi anemia (FA). Babies affected with TAR have absent radii with intact thumbs; babies who have FA exhibit thumb anomalies with or without short radii. Infants who have FA also may manifest short length, small head circumference, and other congenital anomalies. Wiskott-Aldrich syndrome, characterized by thrombocytopenia, a

predominance of small platelets, low IgM concentrations, and eczema, is an X-linked recessive trait that often presents during the first postnatal year with bleeding or infection, although it may be present at birth. Amegakaryocytic thrombocytopenia presents with severe thrombocytopenia without skeletal anomalies, but may be associated with congenital heart disease. Approximately 50% of affected infants suffer severe hemorrhage during the first year after birth, but the mortality rate decreases for infants who survive the first year.

Infants who have Down syndrome are at risk for transient thrombocytopenia or thrombocytosis with or without other cytopenias following birth. Neonatal leukemias often present with skin lesions of extramedullary hematopoiesis, the so-called "blueberry muffin lesions," and almost always exhibit obvious abnormalities in all three cell lines.

### Severe Congenital Disorders of Platelet Function

Glanzmann thrombasthenia (GT) is a severe disorder of platelet function caused by autosomal recessive mutations in the platelet receptor, GP IIb/IIIa, that lead to an absent, quantitatively decreased, or functionally abnormal receptor. GP IIb/IIIa is formed by a heterodimer that associates during platelet activation, forming the fibrinogen receptor that binds activated platelets to form the platelet plug. Infants who have GT have normal platelet numbers, but platelet function, as assessed by PFA-100, template bleeding time, or platelet aggregation, is severely decreased. Affected infants can manifest intracranial, gastrointestinal, retroperitoneal, or skin hemorrhage.

Bernard Soulier (BS) syndrome is a moderately severe autosomal recessive disorder of platelet function caused by genetic mutations in the GP IB/IX receptor that is responsible for platelet adhesion to collagen via the von Willebrand factor. BS is characterized by mild thrombocytopenia and giant platelets.

Infants who have Ehlers-Danlos syndrome, a disorder of collagen, may manifest bleeding in the neonatal period, including ICH. Results of all coagulation screening tests are normal in Ehlers-Danlos syndrome. The template bleeding time is prolonged, but not the PFA-100, because of the incorporation of normal exogenous collagen in the PFA test. Most forms of Ehlers-Danlos syndrome are autosomal dominant. In these cases, a positive family history for joint hyperextensibility, lax skin, impaired wound healing, and early pregnancy loss provide clues to the diagnosis.

## Treatment of Bleeding Related to Congenital Platelet Disorders

Bleeding associated with most significant disorders of platelet number or function require therapy with platelet transfusion. Platelets should be obtained by pheresis to limit the number of donor exposures. Cytomegalovirus-negative products should be used for newborns, if possible. A 10-mL/kg infusion of platelet concentrate should raise the platelet count by about  $50 \times 10^3$ /mL ( $50 \times 10^9$ /L). The half-life of transfused platelets is about 2.5 days in an infant who does not have ongoing consumption. Recombinant activated factor VII (rFVIIa) in doses of approximately 50 mcg/kg has been used successfully to treat bleeding in some infants who have severe platelet dysfunction but normal platelet number. The rationale of rFVIIa use for platelet dysfunction is to limit exposure to donor platelets and avoid platelet refractoriness from sensitization.

## Neonatal Hemophilia and Other Congenital Clotting Factor Deficiencies

Severe factor VIII (FVIII) deficiency affects 1 in 10,000 and factor IX (FIX) deficiency affects 1 in 30,000 live births. Mild FVIII deficiency is diagnosed easily because FVIII concentrations reach adult values by term birth, but because concentrations of FIX can be as low as 15 IU/dL in a term infant, the diagnosis of mild FIX deficiency often must await retesting at 6 to 12 months of age. Deficiencies of both FVIII and FIX are X-linked recessive disorders and affect males almost exclusively. Recent epidemiologic studies have determined clinically manifest ICH in 1% to 4% of infants who have severe deficiency of FVIII or FIX, at least 50% of whom present as probands in families that have a negative history for a bleeding disorder. Vacuum extraction and forceps delivery were used in most infants who had severe hemophilia and suffered ICH, but ICH has been diagnosed in newborns who had hemophilia and were born following cesarean section without labor. Rarely, infants who have severe hemophilia suffer subgaleal hematomas, large caput succedaneum, retroperitoneal hematomas, or subcapsular hemorrhage of the liver or other parenchymal site. However, approximately 50% of infants who have severe hemophilia manifest excessive bleeding following skin puncture for blood sampling or circumcision. The PTT typically is prolonged, and specific assays for FVIII and FIX yield the diagnosis. An occasional infant who has type III von Willebrand disease presents with neonatal bleeding, a prolonged PTT, and low FVIII activity (<10%). For this reason, von Willebrand factor (VWF)

antigen should be determined in all infants whose FVIII activity is less than 10%.

Most rare coagulation factor deficiencies are autosomal recessive and have a reported prevalence of 0.5 to 2 per 1 million population. Absence of fibrinogen (afibrinogenemia) or decreased fibrinogen (hypofibrinogenemia) manifests with bleeding that is similar to that associated with platelet deficiency, involving skin and mucous membranes. Significant bleeding usually is limited to babies whose fibrinogen concentrations are less than 50 mg/dL. Twenty-five percent of persons who have afibrinogenemia develop ICH. FXIII deficiency almost always presents with umbilical cord bleeding. Bleeding with FXIII deficiency usually is associated with FXIII values of less than 5%, and ICH is common in this disorder. FXIII-deficient carriers have a history of deficient and delayed wound healing, and carrier mothers often report increased spontaneous abortion. Diagnosis of FXIII deficiency in an affected infant is extremely important because hemorrhage can be prevented with monthly infusions of FXIII concentrate or cryoprecipitate due to the 10-day half-life of FXIII. Complete deficiency of prothrombin (undetectable FII by a sensitive assay) is incompatible with life and never has been determined in a liveborn infant. Severe FXI deficiency results in variable bleeding, and some genetic mutations that cause homozygous FXI deficiency have presented as nearly asymptomatic. FXII deficiency results in a greatly prolonged PTT but does not cause clinical bleeding. Severe deficiency of the plasminogen activator inhibitor, type 1 (PAI-1) is very rare but is a cause of ICH. Infants who have PAI-1 deficiency have normal coagulation screening test results but manifest uncontrolled fibrinolysis, with a very short euglobulin clot lysis time. Diagnosis of PAI-1 deficiency by plasma assay of PAI-1 activity or antigen is difficult because most commercial assays are insensitive, and the normal pediatric range includes undetectable PAI-1. PAI-1 plasma concentrations demonstrate diurnal variability, with highest values documented in the early morning and lowest values in the late afternoon.

## Treatment of Bleeding Related to Congenital Clotting Protein Disorders

Following the diagnosis of a congenital clotting factor deficiency, it is critical to educate the parents regarding the implications of the diagnosis, treat the bleeding infant with the safest replacement product available, and make provisions for replacement factor availability and infusion prior to hospital discharge. The replacement dose and dosing frequency are calculated based on the

volume of distribution and plasma elimination of the specific factor as well as the severity of the bleeding episode. Recombinant products are ideal for replacement but are not available for all clotting factors. Viral inactivated plasma-derived concentrates are preferable to single-donor blood products because use of products that are not viral-inactivated pose a significant threat of transfusion-related infection over time.

FVIII, VWF, and FXIII distribution are limited to the plasma volume. Therefore, each 1 IU/kg infused raises the plasma concentration by 2%. The average half-life of FVIII or VWF is 12 hours, with the newborn displaying a modest increase in volume of distribution and decrease in half-life. Therefore, plasma concentrations of FVIII or VWF can be raised to normal adult values by administering 50 to 60 IU/kg initially, followed by 25 to 30 IU/kg every 8 to 12 hours. Currently, five rFVIII preparations are available in approximately 250-unit vials. Standard practice involves using a complete vial, unless the given dose can correct the factor to greater than 200%, and then increasing the time between doses. Two plasma-derived concentrates containing VWF and FVIII have a United States Food and Drug Administration (FDA)-approved indication for von Willebrand disease. FXIII has a half-life of 30 days. Babies who have homozygous FXIII deficiency can receive a plasma-derived, viral-inactivated concentrate that is available on an FDA protocol and can be accessed through a hemophilia treatment center or 10 to 20 mL/kg of cryoprecipitate. Recombinant preparations of VWF and FXIII are in development, but not yet commercially available. Local hemophilia treatment centers are the best source of information about current availability.

FIX has a volume of distribution in adults equal to twice the plasma volume. Neonates who have FIX deficiency have been reported to have an enormous volume of distribution and rapid plasma elimination, requiring up to 30 IU/kg per hour to maintain 100% FIX activity. One recombinant FIX is available in the United States. Initial dosing starts at 120 IU/kg bolus, with 60 IU/kg administered every 12 hours.

FVII can be replaced using rFVIIa in doses of 15 to

25 mcg/kg every 3 to 6 hours. Cryoprecipitate is a good source of fibrinogen. Factors XI, X, V, PAI-1, and alpha-1-antiplasmin can be replaced only in fresh frozen plasma. Epsilon-amino-caproic acid, a chemical inhibitor of fibrinolysis, is very useful for babies who are deficient in the physiologic fibrinolytic inhibitors PAI-1 or alpha-1-antiplasmin. Epsilon-amino-caproic acid, in doses of 50 to 100 mg/kg every 6 hours orally, also is useful to maintain clot stability after replacement therapy in babies who have mouth bleeding caused by any factor deficiency.

Bleeding related to ICH requires administration of replacement factor for 6 weeks or more. Major surgery generally necessitates treatment for 14 days or until surgical healing is achieved. Parenchymal bleeding should be treated for at least 10 days because babies who have hemophilia may experience delayed bleeding at 5 to 7 days following the initial hemorrhage. The local hemophilia center is a good resource for treatment of other bleeding sites.

### Vitamin K Deficiency Syndromes

The coagulopathy of vitamin K is one of the most frequent causes of bleeding in otherwise well infants. Neonatal bleeding syndromes related to vitamin K deficiency differ in time of onset and cause (Table 2). Affected infants present with skin, gastrointestinal, and intracranial hemorrhage. Screening coagulation tests in vitamin K deficiency reveal a substantial prolongation of the PT in excess of the PTT. Fibrinogen, D-dimer, platelet count, and PFA are not affected. An immunologic test for noncarboxylated prothrombin, called the PIVKA-II test, is positive. This test rarely is needed to diagnose vitamin K deficiency, but because it remains positive for up to 3 days following treatment with vitamin K, can be valuable to confirm the cause of bleeding in an infant who was treated before diagnostic tests were obtained. Vitamin K should be replaced as 0.5 to 1.0 mg intravenously or intramuscularly, depending on the severity of presentation. Following intravenous vitamin K administration, circulating proteins are not altered, but noncarboxylated proteins that have accumulated within the

Table 2. Vitamin K Deficiency Syndromes

Type	Time of Onset	Cause
Early	First 24 hours after birth	Maternal anticonvulsants, antibiotics
Classic	1 to 7 days after birth	Poor vitamin K intake, usually in breastfed infants
Late	1 to 8 weeks after birth	Fat malabsorption (eg, biliary atresia, cystic fibrosis, alpha-1-antitrypsin deficiency); rarely, antibiotics or poor intake

hepatocytes are carboxylated rapidly and released, causing the PT to shorten substantially within 4 to 6 hours. In cases of life-threatening hemorrhage, rFVIIa 90 mcg/kg or fresh frozen plasma 15 mL/kg can be administered while waiting for PT correction.

In the United States, prophylactic vitamin K is administered to all infants shortly following birth. In cases of suspected or proven vitamin K deficiency, delivery of neonatal vitamin K prophylaxis should be confirmed. One milligram of vitamin K prevents the coagulopathy of vitamin K deficiency for 1 month. Infants who have maternal vitamin K deficiency or inadequate early breastfeeding should not require further vitamin K administration. Infants who have late-onset vitamin K deficiency (ie, beyond age 2 months) should be tested for fat malabsorption related to cystic fibrosis, alpha-1-antitrypsin deficiency, or biliary atresia and may need ongoing replacement.

### Bleeding Related to Liver Failure

Bleeding caused by liver failure in the perinatal period often is fulminant and fatal unless the cause of liver disease can be reversed. The most common sites of bleeding are skin, gastrointestinal, and intracranial, and the most common causes of neonatal liver failure include infection (hepatitis), hypoxia/ischemia, metabolic disorders, and neonatal hemochromatosis. The coagulopathy of liver failure is complex and includes failure of new protein synthesis, consumption of clotting factors and platelets, and inhibition of normal coagulation by faulty clearance of fibrin and fibrinogen degradation products. Liver failure may manifest with abnormalities in all screening tests (Table 1). Extreme prolongation of the PT is related to deficiency of FVII, which indicates acute liver synthesis, due to its very short plasma half-life. The survival of fibrinogen and platelets following transfusion are better indicators of consumption because of their longer plasma circulating half-lives. Treatment of bleeding in liver failure is supportive, and treatment success depends on resolution or reversal of the underlying process. When correction of coagulopathy is required for surgery or an invasive procedure, such as liver biopsy, and PT correction cannot be achieved with fresh frozen plasma, use of rFVIIa in doses of 90 mcg/kg has been reported to be effective in a small number of case reports. Alternatively, correction of deficient clotting factors can be achieved rapidly using plasma exchange. Prior to restoration of adequate liver function, survival of clotting factors may be prolonged without increased bleeding by using very low doses of unfractionated heparin (5 to 10 U/kg per hour).

### Disseminated Intravascular Coagulation

DIC is a syndrome of uncontrolled activation and consumption of platelets and clotting proteins. The coagulation system in DIC is globally impaired, with platelets as well as procoagulant, anticoagulant, and fibrinolytic proteins decreased. The most common causes of DIC in newborns are sepsis, necrotizing enterocolitis, hypoxia/acidosis, and liver failure. In sepsis and necrotizing enterocolitis, platelet consumption is the initial and most prominent abnormality. In DIC related to hypoxia and acidosis, fibrinogen deficiency is more conspicuous. Successful treatment of DIC is indicated by significant improvement in coagulation within 72 hours of initiating therapy and resolution of thrombocytopenia in 7 to 10 days.

In all cases of DIC, treatment of the underlying illness, with attention to oxygenation and circulation, is critical to reverse the coagulopathy. Transfusion support should be provided to maintain minimal hemostatic concentrations of platelets and clotting factors. Fresh frozen plasma may be helpful to replace regulatory and fibrinolytic proteins in addition to procoagulant proteins. The role of replacing specific coagulation regulatory proteins, antithrombin and protein C, or infusions of low-dose unfractionated heparin (5 to 10 U/kg per hour) in severe or refractory DIC has not been proven but could be considered in more difficult cases. Catheter-related and spontaneous thromboses that occur in babies who have DIC should be treated with anticoagulation, with appropriate attention to maintenance of minimal hemostatic concentrations of coagulation proteins and platelets.

### Treatment of Neonatal Bleeding Syndromes

The goal of transfusion therapy in neonatal bleeding disorders is to maintain minimal hemostatic concentrations of key blood components (Table 3). Generally, platelet counts of 10 to  $20 \times 10^3/\text{mcL}$  ( $10$  to  $20 \times 10^9/\text{L}$ ) are hemostatic in a well infant; babies who have sepsis, are undergoing invasive procedures, or require mechanical ventilation may require counts of 50 to  $100 \times 10^3/\text{mcL}$  (50 to  $100 \times 10^9/\text{L}$ ). Pseudothrombocytopenia, caused by platelet clumping, is very common. Thrombocytopenia should be confirmed on a second blood sample prior to instituting platelet replacement therapy. Normal hemostasis requires a fibrinogen concentration of 100 mg/dL and a PT of less than 3 seconds above the upper limit of normal. Such minimal hemostatic values may be maintained using platelet concentrates (10 mL/kg should raise the platelet count by  $50 \times 10^3/\text{mcL}$  [ $50 \times 10^9/\text{L}$ ]), cryoprecipitate (10 mL/kg should raise fibrinogen by 50 mg/dL and

Table 3. Hemostatic Coagulation Values in Newborns

Blood Component	Well, Stable Infant	Sick, Unstable Infant	Replacement	Dose
Platelets	10×10 <sup>3</sup> /mCL (10×10 <sup>9</sup> /L)	50 to 100×10 <sup>3</sup> /mCL (50 to 100×10 <sup>9</sup> /L)	Platelet concentrates	10 mL/kg to attain 50×10 <sup>3</sup> /mCL (50×10 <sup>9</sup> /L) or greater
Prothrombin time	<6 sec above ULN	<3 sec above ULN	Fresh frozen plasma	10 to 20 mL/kg
Fibrinogen	50 mg/dL	100 mg/dL	Cryoprecipitate	10 mL/kg to achieve 50 mg/dL or greater
FVIII	<10%	50% to 100%	Recombinant FVIII	50 U/kg bolus*; may use 2 to 4 U/kg per hour by continuous infusion with laboratory monitoring
FIX	<10%	50% to 100% <sup>†</sup>	Recombinant FIX	100 U/kg <sup>†</sup> ; may require 4 to 40 U/kg per hour to maintain 100%

ULN=upper limit of normal reference value  
 \*Based on a plasma half-life of 6 to 12 hours in newborns, concentrations of FVIII following an initial bolus should be maintained at a minimum of 100% for life-threatening bleeding. This can be achieved using boluses of 25 to 50 U/kg every 8 to 12 hours or by continuous infusion. Laboratory monitoring is essential to confirm the therapeutic range.  
 †Current practice is to replace FIX to 100% of adult concentrations for intracranial or other life-threatening bleeding, although physiologic neonatal concentrations of FIX are 15% to 30%. Due to issues of unique distribution and pharmacokinetics of FIX in the newborn, very high and a very wide range of dosing has been necessary to achieve and maintain plasma FIX at 100% of normal adult values. Laboratory monitoring is essential.

also contains FVIII, VWF, and FXIII), or fresh frozen plasma (10 to 20 mL/kg for all other coagulation factors). After transfusion of a blood product to correct platelet count, fibrinogen concentration, or PT, appropriate laboratory assay should be performed 1 hour following the completion of transfusion to determine initial response and approximately 12 to 24 hours following transfusion to document the duration of response. Determination of degree and duration of response to replacement therapy is critical to plan the timing and dose of subsequent therapeutic interventions.

Single-protein deficiencies should be replaced using the purest, safest product available. Certain clotting proteins have been produced by recombinant technology. Currently, recombinant forms of FVIII, FIX, and FVIIa are available for clinical use. Recombinant forms of FXIII and VWF are in development. Where available, viral-inactivated, plasma-derived protein concentrates are preferable for babies who have genetic clotting protein deficiencies because of the superior viral safety. Currently, viral-inactivated, plasma-derived protein concentrates are available for VWF, FVIII, FIX, antithrombin, and protein C. Concentrates of fibrinogen, FXIII, and FXI are not yet licensed but are available through supervised trials, which are accessed most easily through federally funded hemophilia treatment centers.

rFVIIa has been applied to a wide variety of bleeding emergencies. rFVIIa directly activates factor X, conse-

quently increasing the generation of thrombin. Although a small risk for DIC and thrombosis exists with the use of rFVIIa, preliminary reports of product usage in bleeding newborns have been encouraging. The dosage of rFVIIa is 20 to 25 mcg/kg to replace FVII, 50 mcg/kg to treat bleeding in thrombocytopenia where the platelet count is 30×10<sup>3</sup>/mCL (30×10<sup>9</sup>/L) or greater, and 90 mcg/kg to treat bleeding with coagulopathy.

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## NeoReviews Quiz

8. Clinicians note petechiae and ecchymoses in a 3,250-g healthy term newborn shortly after a spontaneous and uncomplicated vaginal birth. Neonatal alloimmune thrombocytopenia (NAIT) is suspected based on the evidence of antibodies against neonatal platelet antigen PLA-1 detected in maternal serum. Of the following, the *most* accurate statement regarding NAIT is that:
- A. Coagulation assay often shows markedly elevated D-dimer.
  - B. Many cases occur during first pregnancies.
  - C. Repeated platelet transfusions generally are needed.
  - D. Subsequently affected infants tend to have less severe disease.
  - E. Thrombocytopenia often is accompanied by low maternal platelet count.
9. Several gene mutations can cause congenital thrombocytopenia syndromes in the newborn. Some of these syndromes are associated with skeletal defects. Of the following, the thrombocytopenia with absent radius syndrome is *most* likely to be associated with:
- A. Blueberry muffin lesions.
  - B. Congenital heart disease.
  - C. Intact thumbs.
  - D. Microcephaly.
  - E. Skin eczema.
10. Neonatal hemophilia, characterized by severe coagulation factor VIII deficiency, is an X-linked recessive disorder that affects males almost exclusively. Of the following, the *most* common bleeding manifestation in severe neonatal hemophilia is:
- A. Excessive bleeding from circumcision.
  - B. Hemorrhage in joints.
  - C. Retroperitoneal hematoma.
  - D. Subcapsular hemorrhage of the liver.
  - E. Subgaleal hematoma.
11. Coagulopathy associated with vitamin K deficiency is one of the most frequent causes of bleeding in otherwise well newborns. Of the following, the screening coagulation test *most* likely to reveal vitamin K deficiency is:
- A. Fibrinogen concentration.
  - B. Plasma D-dimer.
  - C. Platelet count.
  - D. Platelet function analyzer.
  - E. Prothrombin time.

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