Disorders of Coagulation in the Newborn

Lorena Ostilla, MD,* Karyssa Knopoff, MD,† Patrick Myers, MD,* Perry Morocco, MD†

*Section of Neonatology, Department of Pediatrics, Northwestern University, Chicago, IL

†Section of Pediatric Hematology, Oncology and Stem Cell Transplant, Department of Pediatrics, University of Chicago, Chicago, IL

EDUCATION GAPS

Coagulopathy is common in neonates and can arise from myriad causes. As both congenital and acquired causes can contribute to a coagulopathic state, it is important for clinicians to be able to distinguish between the 2, begin an initial diagnostic evaluation, and initiate treatment promptly.

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

1. Initiate an appropriate initial evaluation for a neonate suspected to have a congenital or acquired coagulopathy.
2. Identify when a neonate has a disorder of primary hemostasis, secondary hemostasis, or a disorder of the fibrinolytic system based on symptoms and laboratory testing.
3. Recognize which common coagulation abnormalities correspond to patterns of laboratory tests.

ABSTRACT

The coagulation system in newborns varies from that of children and adults, with many circulating hemostatic factors being lower in the newborn. Infants are also susceptible to diseases and conditions in the pregnant person affecting their coagulation system, which can make it difficult to rapidly identify the cause behind coagulopathy in a neonate. Coagulation disorders can result in high levels of infant morbidity and mortality, which makes early diagnosis and prompt treatment critical. This review outlines the clinical characteristics, diagnosis and management, epidemiology, and etiologies of both common and uncommon congenital and acquired forms of neonatal coagulopathy.

AUTHOR DISCLOSURES Dr Myers serves on the executive committee for the Council of Pediatric Sub-Specialists and has served as chair of the Organization of Neonatal Training Program Directors. Drs Ostilla, Knopoff, and Morocco have disclosed no financial relationships relevant to this article. This article does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

α2-AP	alpha-2 antiplasmin
aPTT	activated partial thromboplastin time
CMV	cytomegalovirus
DIC	disseminated intravascular coagulation
FVIII	factor VIII
FIX	factor IX
FXIII	factor XIII
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HPA	human platelet alloantigen
HSV	herpes simplex virus
ICH	intracranial hemorrhage
ITP	immune thrombocytopenia
KHE	kaposiform hemangioendothelioma
KMP	Kasabach-Merritt phenomenon
NAIT	neonatal alloimmune thrombocytopenia
PT	prothrombin time
SGA	small for gestational age
TA	tufted angioma
TAR	thrombocytopenia absent radii
VKDB	vitamin K deficiency bleeding disorder
vWD	von Willebrand disease
vWF	von Willebrand factor

The many different proteins and cells that take part in the intricate coagulation system all work toward the goal of homeostasis or hemostasis. A visual representation of the coagulation cascade, including the different pathways and associated laboratory tests, is shown in the Figure. Coagulopathies can broadly be thought of as disorders of primary hemostasis, disorders of secondary hemostasis, or disorders of the fibrinolytic system, with different laboratory values

associated with each disorder (Table 1). Primary hemostasis involves platelet aggregation and the development of the platelet plug in response to vascular injury. (1) Secondary hemostasis is the deposition of insoluble fibrin after activation of hemostatic factors, and the fibrinolytic system is responsible for the dissolution of thrombi. (2)(3) Such disorders can be acquired, in response to medications or other diseases, or can be congenital, arising from genetic mutations and specific deficiencies.

HEMOSTASIS OVERVIEW

Primary hemostasis relies on platelets adhering to areas of vascular injury, attaching to the exposed matrix of collagen and von Willebrand factor (vWF). (1) Platelets then become activated, changing the phospholipids exposed on the cell surface and resulting in platelet aggregation, which subsequently creates the initial platelet plug. (1) Occurring simultaneously is the initiation of the coagulation cascade, or secondary hemostasis, which results in insoluble fibrin generation from a series of protein reactions. (3)(4)(5) This cascade, composed of serine proteases and cofactors, can arise via 2 different pathways, the intrinsic or the extrinsic pathway, which converge on the common pathway.

The extrinsic pathway is triggered when blood makes contact with extravascular cells, which possess tissue factors, resulting in the activation of factor V, which then activates factor X, the first factor of the common pathway. (3)(4) The extrinsic and common pathways are represented in a prothrombin test (PT). (6) In the absence of exposure to tissue factors, the coagulation cascade can also arise from the intrinsic pathway, where the contact system activates after exposure to invasive pathogens and certain materials in the blood. (4)(7) The contact system is composed of factor XII, prekallikrein, and high-molecular-weight kininogen, and reacts to substances including collagen, platelets, and certain bacteria, beginning the cascade. (4)(7)(8) This also ends with activation of factor X, which aids in the generation of thrombin and then fibrin. (4)(5) The intrinsic and common pathways are represented in the activated partial thromboplastin time (aPTT) test. (6) Fibrin is the terminal result of the common pathway, leading to hemostasis and preventing hemorrhage, but this thrombus is then regulated by the fibrinolytic system, which eventually dissolves the thrombus. (2) Plasmin is the primary regulator of fibrinolysis, removing the thrombus when the blood vessel is healed and its integrity is restored. (2)

EPIDEMIOLOGY

Coagulopathy is relatively common in newborns, with adults and children having relatively different coagulation systems than infants. Until an infant has reached 32 weeks' gestational age, their platelet count is reduced compared with older children, and platelet function is decreased. (9) Many coagulation factors are also decreased in neonates, including factors II, VII, IX, X, XI, and XII, antithrombin, and protein C. (9) In contrast, factors V, VIII, and XIII, and fibrinogen have normal levels, whereas vWF is increased. (9)(10) As a result of these alterations, neonates can have up to a 25% chance of bleeding during admission to the NICU, with prematurity increasing risk. (11) One of the most serious bleeding complications includes intraventricular hemorrhage, which can affect 23% of infants born at less than 32 weeks' gestational age, with increasing gestational age being protective. (12) Infants with sepsis, lower birthweight, or the presence of a patent ductus arteriosus have an increased risk. (12)

DISORDERS OF PRIMARY HEMOSTASIS

Impairment of primary hemostasis is frequently responsible for serious bleeding events in infants. Various factors,

Table 1. Diagnosis Based on Coagulation Panel Abnormalities

Type of Disorder	Platelet Count	PT/INR	aPTT
Disorders of Primary Hemostasis			
Quantitative disorders	Decreased	Normal	Normal
Qualitative disorders	Normal or decreased	Normal	Normal
vWD	Normal	Normal	Prolonged
Congenital thrombotic thrombocytopenic purpura	Decreased	Normal	Normal
Collagen and vascular disorders	Normal	Normal	Normal
Disorders of Secondary Hemostasis			
Vitamin K deficiency	Normal	Prolonged	Normal or prolonged
Hemophilia A: Factor VIII deficiency	Normal	Normal	Prolonged
Hemophilia B: Factor IX deficiency	Normal	Normal	Prolonged
Factor XIII deficiency	Normal	Normal	Normal

aPTT=activated partial thromboplastin time, INR=international normalized ratio, PT=prothrombin time, vWD=von Willebrand disease.

including heredity, maternal acquisition, infections, and drugs, can impair primary hemostasis in the neonate. Gestational age (premature infants typically exhibit slightly lower platelet counts compared with those born at full term), hypoxia, acidosis, higher vWF concentrations and enhanced function, lower plasma level and activity of other coagulation proteins, elevated hematocrit count, large erythrocytes during the first day after birth, and platelet hyperreactivity are other factors to consider. (9)(10) In addition to an accurate medical and family history, physical examination, coagulation testing, and potential hematology consultation can help identify a disorder of primary hemostasis (Table 2 and Table 3).

Quantitative Disorders of Primary Hemostasis

Impaired Platelet Production. Platelets are formed through the fragmentation of megakaryocytes in the bone marrow. This process begins during early fetal life and increases in number to adult concentrations in the peripheral blood around 22 weeks' gestation. (13) Newborns have developmental

Table 2. Quantitative Disorders of Primary Hemostasis

Disorder	Pattern of Inheritance/ Transmission	Clinical Signs and Symptoms	Diagnosis	Management
Neonatal alloimmune thrombocytopenia	Transfer of platelet-specific antibodies	Thrombocytopenia Risk of bleeding ICH is common	Platelet count Plasma levels of anti-HPA-1A in parents	Donor-matched platelet transfusion Intravenous IgG
Immune thrombocytopenia in the birthing parent	Transfer of platelet-specific antibodies	Thrombocytopenia Risk of bleeding ICH is rare	Birthing parent and infant platelet counts	Intravenous IgG Corticosteroids
Thrombocytopenia from preeclampsia	N/A	Maternal hypertension with or without thrombocytopenia Low birth weight infant	Clinical history and platelet counts	Platelet transfusion
Congenital infection	Congenital or perinatal transmission	Variable: • Toxoplasmosis: petechiae, hepatosplenomegaly, jaundice, low birth weight, hydrocephalus, intracranial calcifications, microcephaly • Rubella: microcephaly, developmental delay, hearing impairment, hepatosplenomegaly, retinopathy, congenital glaucoma, cataracts, intrauterine growth restriction, congenital heart defects, and purpura • CMV: sensorineural hearing loss, microcephaly, intracranial calcifications, hepatitis, purpura, retinitis and severe thrombocytopenia • HIV: sepsis, growth faltering • HSV: sepsislike illness, thrombocytopenia, consumptive coagulopathy, and acute liver failure	Clinical manifestations with viral or infectious disease testing	Antiviral or antibacterial treatments
Thrombocytopenia absent radii syndrome	Autosomal recessive	Bleeding and thrombocytopenia that improves over time May have cardiac and renal abnormalities	Clinical manifestations Genetic testing	Platelet transfusion
Wiskott-Aldrich syndrome	X-linked recessive	Thrombocytopenia Eczema Immunodeficiency	Genetic testing	Intravenous IgG Platelet transfusion Corticosteroids
Congenital amegakaryocytic thrombocytopenia	Autosomal recessive	Purpura, petechia, and bleeding (early) Aplastic anemia and leukemia (late)	Bone marrow biopsy Genetic testing	Platelet transfusion Stem cell transplant

CMV=cytomegalovirus, HIV=human immunodeficiency virus; HSV, herpes simplex virus, ICH=intracranial hemorrhage, Ig=immunoglobulin, N/A=not applicable.

Table 3. Qualitative Disorders of Primary Hemostasis

Disorder	Pattern of Inheritance/ Transmission	Clinical Signs and Symptoms	Diagnosis	Management
Glanzmann thrombasthenia	Autosomal recessive	Mild to severe bleeding	Flow cytometry with the absence of GPIIb/IIIa receptor Platelet aggregation studies	Factor VIIa Aminocaproic acid Platelet transfusion
Bernard-Soulier syndrome	Autosomal recessive	Mild to severe bleeding	Flow cytometry: absence of glycoprotein IB, V, and IX on platelet surfaces and platelet aggregation studies	Platelet transfusion
Gray platelet syndrome	Autosomal dominant, autosomal recessive, or X-linked	Bleeding Splenomegaly	Peripheral smear review and no α-granules on electron microscopy	Platelet transfusion Desmopressin Splenectomy
Hermansky-Pudlak syndrome	Autosomal recessive	Bleeding Oculocutaneous albinism Vision abnormalities Possible immunodeficiency	Clinical findings Lack of platelet δ granules on electron microscopy	Platelet transfusion Desmopressin
von Willebrand disease	Autosomal dominant (type 1 and most type 2) or autosomal recessive (type 3)	Frequent mucocutaneous bleeding, with spontaneous joint or muscle bleeding and/or hematomas in type 3 disease	aPTT and FVIII activity vWF ristocetin-cofactor activity vWF antigen levels	Antifibrinolytics, desmopressin vWF concentrates alone and/or a combination of FVIII:vWF
Congenital thrombotic thrombocytopenic purpura	Autosomal recessive	Hyperbilirubinemia Thrombocytopenia Stroke and other arterial thromboembolic events, ischemia, and renal disease	ADAMTS13 activity	ADAMTS13 replacement
Collagen and vascular disorders	Typically autosomal dominant	Bleeding Skin and joint hypermobility (Ehlers-Danlos syndrome) Arteriovenous malformations Telangiectasis (hereditary hemorrhagic telangiectasia)	Clinical and family history	Antifibrinolytics

aPTT=activated partial thromboplastin time, FVIII=factor VIII, vWD=von Willebrand disease.

immaturities in hematopoiesis and are thus more susceptible to peripheral cytopenia, particularly in high-demand states, if they have defects in thrombopoiesis and myelopoiesis. For instance, prolonged intrauterine hypoxia resulting from placental dysfunction might cause both thrombocytopenia and polycythemia in small-for-gestational-age (SGA) newborns owing to impaired thrombopoiesis. (14) Multiple studies indicate that plasma concentrations of thrombopoietin, which controls thrombopoiesis, are elevated in both full-term and preterm neonates compared with healthy adults. (15) Conversely, neonatal megakaryocyte progenitors may have higher proliferative rate potential and more sensitivity to thrombopoietin than adult progenitors. (16) However, compared with adult megakaryocytes, they produce fewer platelets per cell and are smaller. (17)

In normal circumstances, the adult bone marrow adapts to heightened platelet requirements by enlarging megakaryocytes and increasing their ploidy, thereby boosting megakaryocyte mass. (18) However, neonates with thrombocytopenia can augment the quantity of their megakaryocytes but are unable to affect their size. (18) A small neonatal megakaryocyte may thus have limited ability to respond to increased demand and thrombocytopenia. (18)

When platelets adhere to areas of vascular damage, they release biological mediators and the contents of granules to facilitate plasma coagulation reactions. (1) Following endothelial damage, platelets attach to the underlying basement membrane collagen, initiating the primary stage of hemostasis and engaging with subendothelial vWF. (1) Glycocalicin serves as an indicator of heightened platelet turnover, whereas interleukin 6 levels rise in reaction to thrombocytopenia. (19) Neonates experiencing intrauterine growth restriction and thrombocytopenia exhibited undetectable levels of glycocalicin in their plasma, indicating compromised thrombopoiesis. (19) In addition, alloimmunization

against platelets can occur during pregnancy or after receiving a transfusion, resulting in the swift destruction of incompatible platelets. (20)

Neonatal Alloimmune Thrombocytopenia. Neonatal alloimmune thrombocytopenia (NAIT) is rare (1 in 1,000 births) and is triggered by the transfer of platelet-specific alloantibodies or human leukocyte antigen antibodies from the pregnant person across the placenta, which then recognize the corresponding antigens in the infant. (21) The human platelet alloantigens (HPAs) from the non–birth parent may differ from those of the birth parent, leading to the production of antibodies in the pregnant person against an unfamiliar antigen. As early as 15 weeks of gestation, these immunoglobin G antibodies can be transplacentally transmitted to the fetal circulation, causing thrombocytopenia, and can persist until they are cleared. (22)(23) The likelihood of NAIT recurring in subsequent pregnancies has been projected to exceed 80%, with subsequent presentations having greater severity and an increased risk of bleeding. (24)

NAIT is diagnosed based on clinical and serologic findings. Clinical findings related to thrombocytopenia include ecchymosis, petechiae, purpura, and bleeding. Intracranial hemorrhage (ICH) stands out as one of the most critical complications and can be detected during pregnancy as early as the 20th week of gestation. (25) However, NAIT frequently remains undetected during prenatal screening because universal screening is not routinely conducted. Screening tools include the detection of plasma levels of anti-HPA-1a, the most common antigen involved in white pregnant persons. (24) Fetal HPA genotyping through amniocentesis is rarely used given the invasive nature of the procedure. (24)

Postnatally, NAIT should be considered in a newborn with thrombocytopenia within 48 hours of delivery after excluding other factors contributing to thrombocytopenia. The birth parent's platelet count should be obtained if a neonate has thrombocytopenia without an identified cause because it can distinguish NAIT from other autoimmune thrombocytopenias such as immune thrombocytopenia (ITP). (24) Final diagnosis can then be made with platelet immunologic testing of both parents. (24) In addition to this testing, anti-HPA antibodies in blood in the birth parent and genotyping in the non–birth parent can identify the risk of recurrence in subsequent pregnancies. (23)(24)

For prenatal management, intravenous immunoglobin with or without steroid administration is the preferred treatment and can be given to pregnant persons as early as 18 weeks' gestation. (24) Fetal platelet counts can be measured through cordocentesis, with findings of severe thrombocytopenia warranting treatment. (24) Postnatally, infants with platelet counts less than $50 \times 10^3/\mu L$ ($50 \times 10^9/L$) should be screened for ICH with head ultrasonography and given a platelet transfusion if platelets fall below $30 \times 10^3/\mu L$ ($30 \times 10^9/L$). (24) The threshold for transfusion decreases if the newborn is actively bleeding or has an intracranial or extracranial hemorrhage, and it is important not to postpone treatment while waiting for confirmation testing. (24) Infants should be given donor-matched platelet transfusions, because antibodies from the birth parent might persist in the infant's bloodstream, and platelets may not stabilize until these antibodies are cleared from the infant's circulation. (24) In addition, intravenous immunoglobin may be necessary while antibodies are cleared. (24)

ITP in the Pregnant Person. ITP in the pregnant person causes neonatal thrombocytopenia because of active transplacental transport of antiplatelet antibodies from the pregnant person, which then act against fetal platelet surface glycoproteins. In ITP, platelet counts in the birth parent are low whereas infant platelet counts are variable. If platelet counts in the infant are initially decreased, platelets should continue to be monitored after birth as platelet counts may continue to fall postnatally. (26) Platelet counts will typically normalize by 4 to 6 weeks after birth. (26) Thrombocytopenia is significant enough in 9% to 15% of infants born to persons with ITP that treatment is required but fortunately, only 0% to 1.5% of infants have ICH. (26) Infants with platelet counts less than $50 \times 10^3/\mu L$ ($50 \times 10^9/L$) may need to be monitored even though the risk for ICH is low. (26)

Congenital Neonatal Infections.

Cytomegalovirus

Cytomegalovirus (CMV) can cause neonatal infection from congenital or perinatal transmission, and can manifest as sensorineural hearing loss, microcephaly, intracranial calcifications, hepatitis, pneumonia, purpura, retinitis, SGA, and severe thrombocytopenia. Diagnosis is achievable by detecting CMV in both urine and saliva of the neonate through polymerase chain reaction, with sensitivities ranging from 93% to 100%. (27) Pregnant persons with mononucleosislike illness and/or with fetal anomalies suggestive of congenital CMV should be tested. (27)(28) Treatment includes 6 months of valganciclovir therapy in newborns showing symptoms with CNS involvement between 32 weeks' gestation and less than 1 month of age. (28) It is important to monitor for myelosuppression during the full course of treatment. (28)

Toxoplasmosis

Neonatal toxoplasmosis presents with petechiae, hepatosplenomegaly, jaundice, low birthweight, hydrocephalus, intracranial calcifications, microcephaly, seizures, retinitis, and microphthalmia. (29) Diagnosis is achieved through anti-*Toxoplasma gondii* immunoglobulin (Ig)M/IgA and IgG, indirect ophthalmoscopy to identify retinochoroiditis, and the detection of calcification and hydrocephalus via brain magnetic resonance imaging and computed tomography. (30) If pregnant persons are diagnosed during gestation through serologic or amniotic fluid testing, treatment with spiramycin can be offered early in pregnancy, or pyrimethamine and sulphonamide in the third trimester through delivery. (30) In the infant, therapy includes a combination of pyrimethamine and sulfonamide for 12 months. (30) It is important to monitor for bone marrow suppression throughout the treatment course because of folate metabolism inhibition. (30)

Rubella

Congenital rubella syndrome is an uncommon cause of thrombocytopenia in infants. Clinical characteristics include microcephaly, developmental delay, hearing impairment, hepatosplenomegaly, retinopathy, congenital glaucoma, cataracts, intrauterine growth restriction, congenital heart defects, and purpura. (31) Thrombocytopenia can be secondary to bone marrow suppression (particularly in SGA infants) but the exact etiology remains unknown. (32)

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) type 1 infection remains a major contributor to morbidity and mortality among children in low- and middle-income nations, with over a third of HIV-1–positive infants succumbing to the infection during childhood if left untreated. (33) Thrombocytopenia, sepsis, and failure to thrive have been identified as common findings in symptomatic patients. (34) Early diagnosis and immediate treatment via the initiation of antiretroviral therapy are imperative and critical for children younger than 18 months who have been exposed to perinatal HIV-1. Diagnosis is established by using molecular virologic assays, such as HIV-RNA or HIV-DNA tests. (33)

Herpes Simplex Virus

In infants, herpes simplex virus (HSV) infection can present as a widespread or disseminated disease affecting various organs, localized central nervous system involvement with or without skin symptoms, or infection restricted to the skin, eyes, and/or mouth. (35) Symptoms of HSV infection may appear any time from birth to 6 weeks of age, but infants with disseminated disease typically experience an earlier onset and present with symptoms resembling sepsis. (35) The infant may have thrombocytopenia, consumptive coagulopathy, and acute liver failure within the initial 30 days after birth. (35) Diagnosis is completed through HSV polymerase chain reaction assays from any skin vesicles, cerebrospinal fluid, whole blood, and surface swabs of the conjunctiva, nasopharynx, mouth, and anus. (35) When HSV infection is suspected or confirmed, prompt treatment with intravenous acyclovir should be initiated.

Preeclampsia. With an incidence of 2% to 6% in the United States, preeclampsia is the most common pregnancy-related complication in pregnant patients. (36) Its primary pathologic characteristics result from the activation of platelets and a widespread ischemic disorder due to endothelial dysfunction. Mechanisms considered for the etiology of thrombocytopenia include decreased platelet production and decreased circulating megakaryocyte progenitors, as well as increased immune-mediated platelet consumption. (36) Thrombocytopenia is observed in SGA infants, possibly stemming from consumptive coagulopathy, platelet destruction, and vascular pathology. (36) In SGA newborns, elevated erythropoietin levels and impaired thrombopoiesis may be the result of intrauterine hypoxia. (14) In addition, infants born to persons with preeclampsia have significantly lower platelet counts, lower megakaryocyte colony-forming units, and decreased megakaryocyte counts. (36)

Congenital Thrombocytopenia Syndromes. Congenital thrombocytopenia syndromes should be considered in infants who present with bleeding near birth that is out of proportion to their thrombocytopenia, have an associated family history, and have additional nonhematologic clinical findings. Thrombocytopenia absent radii (TAR), amegakaryocytic thrombocytopenia, and Wiskott-Aldrich syndrome are the primary platelet disorders with these manifestations but rare inborn errors of metabolism, such as Gaucher disease and methylmalonic acidemia, can also be considered. (26)

TAR is an autosomal recessive disorder in which infants have bilateral absent radii with thumbs and present with bleeding, petechial rash, and purpura near the time of birth. (37)(38) Bleeding and thrombocytopenia are more severe early in life and will often improve as the infant grows older. (38) Infants with TAR are predisposed to cow milk intolerance, which temporally correlates to worsening thrombocytopenia. (38) Both cardiac and renal abnormalities can be seen as part of TAR. (38) The diagnosis is

established through clinical observations, which can be validated via genetic testing.

Congenital amegakaryocytic thrombocytopenia is inherited in an autosomal recessive fashion with severe (type 1) and mild to moderate (type 2) types. (39)(40) Purpura, petechiae, and bleeding can occur in the first month of age. (39)(40) Other hematologic manifestations include aplastic anemia and leukemia as a late manifestation. (39)(40) Bone marrow biopsy will show a reduction in megakaryocytes, and genetic testing of the *c-MPL* gene will lead to a definitive diagnosis. (39)(40) At present, hematopoietic stem cell transplantation stands as the only curative treatment option. (41)

Wiskott-Aldrich syndrome has the clinical hallmarks of thrombocytopenia, eczema, and immunodeficiency, with an X-linked recessive inheritance pattern. (42) The small platelets and thrombocytopenia are thought to be due to splenic destruction. (42) Infants can have failure to thrive and are susceptible to infections from encapsulated organisms. (42) Treatments may include intravenous immunoglobulin, platelet transfusions, and corticosteroids. (42)

Medications. Medications can also be a cause of quantitative platelet disorders, particularly in well-appearing infants with no other identified causes of thrombocytopenia. Common causes include antibiotics, heparin, phenytoin, and indomethacin. (26)(37)

Qualitative Disorders of Primary Hemostasis

Qualitative Platelet Disorders. Although rare, inherited qualitative platelet disorders should be considered in infants with early-onset bleeding that is persistent and disproportionate to the platelet count, and with an abnormal peripheral blood smear. There may be a family history of autosomal dominant, autosomal recessive, or X-linked inheritance. On peripheral blood smear, platelets can be large or have abnormal morphology. (37) Definitive diagnosis can be challenging, with platelet function testing, flow cytometry, and genetic testing all being used. Some qualitative platelet disorders, such as Glanzmann thrombasthenia and Bernard-Soulier syndrome, carry an increased risk for isoimmunization or alloimmunization after platelet transfusions leading ultimately to ineffective platelet transfusions. (37)

Glanzmann thrombasthenia is an autosomal recessive quantitative or a qualitative platelet disorder. It is found more frequently in certain ethnic groups and consanguinity. (37) The clinical signs of bleeding vary in severity, from mild to potentially life-threatening. (37) Platelet transfusions are the mainstay of treatment, with factor VIIa and aminocaproic acid for mucosal hemorrhages. (37) Both platelet morphology and numbers are normal during evaluation, and identification of defects in platelet glycoprotein IIB/IIIa leads to a definitive diagnosis. (37)

Bernard-Soulier syndrome causes bleeding due to large platelets that have poor adhesion. (37) It has an incidence of less than 1 per million and can manifest in infancy, though 16 years is the mean age of diagnosis. (37)(43) Affected patients can have severe life-threatening hemorrhage with an estimated 16% mortality rate but can also have only unexplained purpura. (43) Life-threatening hemorrhage may be out of proportion to their thrombocytopenia. (37) Platelet transfusions are the mainstay of treatment, and definitive diagnosis is via flow cytometry, showing an absence of glycoprotein IB, V, and IX on platelet surfaces. (37)(43)

Gray platelet syndrome is named after the appearance of the washed-out gray platelets seen on peripheral smears. It is caused by an absence of platelet α-granules which leads to bleeding, splenomegaly, and myelofibrosis. (44) Genetic inheritance can be autosomal dominant, autosomal recessive, or X-linked. (44) Patients present with bleeding diathesis near the time of birth, easy bruising, and low platelet counts. (44) Diagnosis is made by the appearance of large, gray washed-out platelets on peripheral smear and the lack of α-granules on the electron microscope. (37)(44)

Inherited via an autosomal recessive pattern, patients with Hermansky-Pudlak syndrome present with bleeding diathesis, oculocutaneous albinism, vision abnormalities, and in some variants, immunodeficiency and neutropenia. (45) Additional clinical findings are postprocedural bleeding, easy bruising, and colonic bleeding and may include ocular conditions (ie, nystagmus, strabismus), pulmonary fibrosis, and granulomatous colitis. (45) The diagnosis is clinical, with additional findings of impaired secondary aggregation, and the absence of platelet δ granules (dense bodies) on an electron microscope. (37)(45)

Von Willebrand Disease. Von Willebrand disease (vWD) is the most prevalent hereditary bleeding disorder and results from an anomaly in vWF, a glycoprotein essential for platelet adhesion to the subendothelium following vascular injury. (1) In addition, vWF stabilizes factor VIII (FVIII) in the coagulation cascade, shielding it from degradation. (46) Inheritance is autosomal dominant for type 1 vWD and most forms of type 2, and autosomal recessive for type 3. (46) Type 1, a quantitative defect, is the most common form, but can have a range of clinical severity. (46)(47) If symptomatic, the initial presentation includes frequent mucocutaneous bleeding, with spontaneous joint or muscle bleeding and/or hematomas in type 3 disease. (46)

Diagnosis is made through measurement of aPTT and FVIII activity, vWF ristocetin-cofactor activity, and vWF antigen levels. Therapies include tranexamic acid, desmopressin, high-purity vWF concentrates alone, and/or a combination of FVIII:vWF, based on the severity of the disease. (46) There is a relative contraindication to the use of desmopressin in children younger than 2 years, but it may be considered if accompanied by careful management with fluid restriction, prevention of hyponatremia, and monitoring of both electrolyte levels and urine output. (46)

Thrombotic Thrombocytopenia Purpura. Congenital thrombotic thrombocytopenia purpura is a rare autosomal recessive inherited condition of ADAMTS13 metalloprotease deficiency. (48) Symptoms include hyperbilirubinemia, thrombocytopenia, stroke and other arterial thromboembolic events, ischemia, and renal disease. (48) Treatment with ADAMTS13 replacement reduces the incidence of end-organ damage. (48)

Collagen and Vascular Disorders. Collagen is a key component of basement membrane function and provides structural support for cellular behavior and signaling. Mutations in collagen IV, VI, VII, XV, XVII, and XVIII are rare but cause diseases affecting multiple systems. (49) Collagen IV mutations, being the most prevalent structural basement membrane element, can lead to a range of multisystemic disorders, encompassing cerebral small vessel disease, intracerebral hemorrhage, kidney disorders, ocular abnormalities, and myopathy. (49)

Distinguishing features of other inherited connective tissue disorders such as Ehlers-Danlos syndrome, consist of susceptibility to easy bruising and bleeding. This arises from mutations in the genes for fibrillar collagen proteins (collagen type I, III, and V) and presents with skin and joint hypermobility, spontaneous hematomas secondary to minimal trauma, delayed wound healing, and fragility of the blood vessels and internal organs. (50)

Hereditary hemorrhagic telangiectasia, also known as Osler-Weber-Rendu syndrome, is a genetic disorder inherited in an autosomal dominant pattern, characterized by bleeding resulting from abnormal blood vessels. (51) Patients usually have subclinical arteriovenous malformations in the lungs and liver, and carry a high risk for bleeding and other complications including pulmonary hypertension and hemorrhagic stroke. (51) Other symptoms include epistaxis, anemia from gastrointestinal bleeding, and telangiectasias of the lips, fingertips, and buccal mucosa. (51)

DISORDERS OF SECONDARY HEMOSTASIS

Secondary hemostasis refers to the process of fibrin formation via the coagulation cascade, primarily involving coagulation factors and activated cell surfaces. Diagnosis of inherited bleeding disorders affecting secondary hemostasis relies on a combination of coagulation tests, family history, and clinical history (Table 4).

Hemophilia A: Factor VIII Deficiency

Hemophilia A is a hereditary coagulation disorder linked to the X chromosome, resulting from a deficiency in FVIII, with an incidence of around 1 in 5,000 males. (52) Approximately 30% of mutations arise de novo, therefore absence of a family history does not exclude the possibility of the condition. (53)

Table 4. Disorders of Secondary Hemostasis

Disorder	Pattern of Inheritance/ Transmission	Clinical Signs and Symptoms	Diagnosis	Management
Hemophilia A: factor VIII deficiency	X-linked recessive or de novo mutations	Bleeding episodes, often involving joints and muscles, circumcision site bleeding, ICH is rare.	Prolonged aPTT Low factor VIII level	Desmopressin Factor VIII replacement Non-factor therapies
Hemophilia B: factor IX deficiency	X-linked recessive	Frequent bleeding episodes in the neonatal period, muscle and joint bleeding, occasional spontaneous hemorrhages	Prolonged aPTT Low factor IX level	Factor IX replacement
Factor XIII deficiency	Autosomal recessive	Skin bruising, subcutaneous bleeding, bleeding from the umbilical cord, ICH, and soft tissue hematomas	Low Factor XIII level Normal PT, aPTT, and platelet count	Fresh-frozen plasma or cryoprecipitate Factor XIII replacement
Vitamin K deficiency	Prevented by vitamin K prophylaxis at birth	Bleeding through the umbilical cord/stump, cephalohematoma, ICH, gastrointestinal and mucocutaneous bleeding	Prolonged PT with or without aPTT elevation Normal platelets and fibrinogen	Administration of a parenteral dose of vitamin K

aPTT=activated partial thromboplastin time, ICH=intracranial hemorrhage, PT=prothrombin time.

A suspected diagnosis due to bleeding episodes, often involving joints and muscles, or a family history, should prompt further testing. A prolonged aPTT alongside a normal PT and platelet count is typical of hemophilia A. (54) Severity is based on factor level compared with normal, with mild being 5% to 40%, moderate 1% to 5%, and severe less than 1%. (54) The earliest and most serious complication in neonates with severe hemophilia is ICH, which occurs in 1% to 4% of cases. (54) Extracranial hemorrhage, including subgaleal bleeding and cephalohematoma formation, can also occur. (53)(54) Circumcision site bleeding is common and severe hemophilia can present with spontaneous muscle hemorrhage in the lower extremities, iliopsoas muscle buttocks, and forearms, as well as intra-articular bleeding. (54)

Treatment goals are to achieve hemostasis during acute bleeds and avoid rebleeding. Desmopressin is the preferred hemostatic treatment of individuals with mild disease along with early rehabilitation and pain management. (54) ICH should be suspected with new hypertension, change in mental status or level of alertness, lethargy, or increased fussiness, and treated accordingly. For moderate to severe disease, and for joint bleeds, consecutive days of factor replacement is required. (54) Other novel therapies have become available and include nonfactor therapies and gene therapy. (54)

Hemophilia B: Factor IX Deficiency

Hemophilia B is a rare genetic bleeding disorder linked to the X chromosome, characterized by a deficiency in coagulation factor IX (FIX), occurring in 5 in 100,000 males. (54) Clinical bleeding often corresponds with the levels of FIX activity in the plasma, but certain patients may exhibit variability in the severity of bleeding symptoms. (54) Disease severity is based on the same thresholds as hemophilia A, with severe being less than 1% of normal. (54) If severe, presentation is similar to severe hemophilia A, with frequent bleeding episodes in the neonatal period. (54) Patients with mild to moderate hemophilia B have a wider bleeding phenotype, ranging from bleeding with minor trauma to more severe muscle and joint bleeding and occasional spontaneous hemorrhages. (54)

At birth, there is a reduction in all vitamin K–dependent factors, including FIX, and this reduction is even more pronounced in preterm neonates, posing challenges in diagnosing hemophilia B at birth. (9)(10) Diagnosis can be made by measuring plasma FIX activity levels; genetic analysis is then recommended to establish a causative mutation. (54)

The goal of treatment involves exogenous FIX concentrates to achieve hemostasis and prevent recurrent bleeding and joint destruction. Prophylactic treatment entails regular administration of FIX concentrate to maintain a minimum trough FIX activity of 1% between doses. (54) Emerging treatment approaches for hemophilia include subcutaneous FIX products and gene therapy based on adeno-associated viral vectors. (54)

Factor XIII (FXIII) Deficiency

Congenital FXIII deficiency is a rare autosomal recessive bleeding disorder, affecting roughly 1 in 2 million individuals. (55) Activated FXIII is critical in the final phase of coagulation by enhancing the stability of the fibrin clot. (2) Symptoms can vary from severe, potentially life-threatening bleeding to milder manifestations such as skin bruising, subcutaneous bleeding, bleeding from the umbilical cord, and soft tissue hematomas. Patients with FXIII deficiency will initially form a clot, but this will be unstable and they will have rebleeding. (55) The severity of bleeding is associated with the level of FXIII activity and the severe phenotype has the highest rate of ICH of any bleeding disorder. (56) Diagnosis is difficult because PT, aPTT, platelet count, and thrombin time are normal; specific FXIII assays are required for the diagnosis. (57) In the event of acute bleeding, fresh-frozen plasma or cryoprecipitate can be given if the diagnosis is suspected. If the diagnosis is made, treatment is factor infusions.

Vitamin K Deficiency

Vitamin K deficiency bleeding disorder (VKDB) was initially identified in the 1800s as a hemorrhagic disease of the newborn. (58) In 1961, the American Academy of Pediatrics, recommended that all infants be given a single parenteral dose of vitamin K at birth, which has dramatically reduced the mortality rate of VKDB and the incidence of ICH. (58)(59)

VKDB should be considered in all infants who present with a bleeding diathesis in the first 6 months of age. Newborns are particularly vulnerable to deranged vitamin K metabolism because of limited vitamin K acquisition during gestation and initial lack of gut flora to produce additional vitamin K. (60) ICH, a bleeding umbilical stump, gastrointestinal and mucocutaneous bleeding, and bleeding circumcisions should prompt the clinician to consider the possibility of VKDB. (58)(60)

The etiology and time frame of VKDB is divided into early, classic, and late presentations. Early VKDB occurs in the first 24 hours after birth and is secondary to the

transplacental acquisition of drugs from the pregnant person that interfere postnatally with the infant's metabolism of vitamin K. (58)(60) Clinical findings consist of cephalohematoma, umbilical stump bleeding, and ICH with a history of medications administered to the pregnant person that reduce the infant's available vitamin K, such as warfarin, anticonvulsants, and antituberculosis medications. (58)(60)

Classic VKDB occurs between 2 and 7 days after birth and arises from insufficient vitamin K intake in newborns. (58)(60) In addition to the impact of medications taken by the pregnant person, classic VKDB deficiency occurs in infants who exclusively drink breast milk, have limited enteral intake, and have received inadequate vitamin K supplementation (ie, zero vitamin K or a single oral dose) at birth. (58) The birth parents of infants with classic VKDB will often have a diet that is low in vitamin K, which occurs in green, leafy vegetables. (60)

Late VKDB manifests between 2 weeks and 6 months of age with ICH and gastrointestinal and mucocutaneus bleeding. (58)(60) Infants with an exclusive mother's own milk diet continue to be at higher risk of late VKDB as well as infants with poor absorption of vitamin K. (60) This includes infants with prolonged diarrhea, liver disease, pancreatic insufficiency, cystic fibrosis, and biliary atresia. (58)(60) Late VKDB has an increased risk in the summer months and in male infants. (58)(60)

A prolonged PT increases suspicion for VKDB, though if the duration is sufficient, aPTT may be increased as well. (60) If both are prolonged, the PT prolongation will be out of proportion to the aPTT. (37)(60) Factor II, VII, IX, and X concentrations will be decreased while platelets and fibrinogen are normal. (37)(58)(60) Head imaging should be conducted to assess for possible ICH.

Management of the acute complications of VKDB consists of administration of a parenteral dose of vitamin K. With adequate treatment, PT and aPTT corrects in 2 to 6 hours, which helps to confirm the diagnosis. (60) As prophylaxis, term infants should receive a single dose of 0.5 to 1.0 mg of vitamin K whereas preterm infants should receive a dose of 0.3 to 0.5 mg/kg if birthweight is below 1,000 g. (58) Oral prophylaxis is less efficacious than intramuscular prophylaxis because of lower parental compliance and inconsistent drug absorption. (58)

DISORDERS OF FIBRINOLYSIS

Qualitative/Quantitative Fibrinogen Disorders

Fibrinogen is a glycoprotein synthesized by the liver and present in the plasma. Rare mutations can lead to either quantitative (type 1) deficiencies or qualitative (type 2) dysfunctional proteins, from 3 possible genes (*FGA, FGB,* and *FGG*). (61) The rarest form, afibrinogenemia, usually manifests during infancy, with prolonged bleeding seen after circumcision and bleeding from the umbilical cord. (61)

Nearly all instances of afibrinogenemia result from null mutations in the *FGA* gene. (62) Although bleeding is the more common manifestation, thrombosis can also occur because of the impaired antithrombin function of fibrin. (61) Hypofibrinogenemia and dysfibrinogenemia disorders are associated more commonly with mild bleeding tendencies, but most patients are asymptomatic and are incidentally identified on abnormal screening coagulation tests. (61) Most hypofibrinogenemias are missense mutations found equally in all 3 genes whereas dysfibrinogenemias are mainly missense mutations in genes *FGA* and *FGG*. (61)

Fibrinogen concentrate, cryoprecipitate, or fresh-frozen plasma is most used in patients with afibrinogenemia and hypofibrinogenemia, whereas antifibrinolytic drugs (ie, aminocaproic acid and tranexamic acid) are used more frequently in dysfibrinogenemia. (61)

Plasminogen Activator Inhibitor 1 Deficiency

Plasminogen activator inhibitor 1 (PAI-1) functions as a urokinase-type plasminogen activator and inhibits tissue-type plasminogen activator as a protease inhibitor. PAI-1 inhibits fibrinolysis, but when absent or nonfunctional, clots are unstable and prematurely break down. (62) Bleeding typically only happens as a result of surgical procedures or trauma, though it can be serious and life-threatening, and difficult to predict as PT and aPTT are normal. (62) Medications like tranexamic acid and aminocaproic acid, which inhibit fibrinolysis, are successful in both treating and preventing instances of bleeding. (62)

α-2 Antiplasmin Deficiency

α-2 Antiplasmin (α2-AP) is another protease inhibitor of fibrinolysis which acts as a primary inhibitor of plasminogen. (2) Fibrinolysis takes place when activating agents act on plasminogen to transform it into the active serine protease plasmin, predominantly tissue plasminogen activator. α2-AP deficiency is an autosomal recessive condition. (63) Aminocaproic acid and tranexamic acid, alongside other inhibitors of fibrinolysis, can be beneficial in treatment. (63)

ACQUIRED COAGULOPATHIES

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a multifactorial condition involving coagulation and immune and

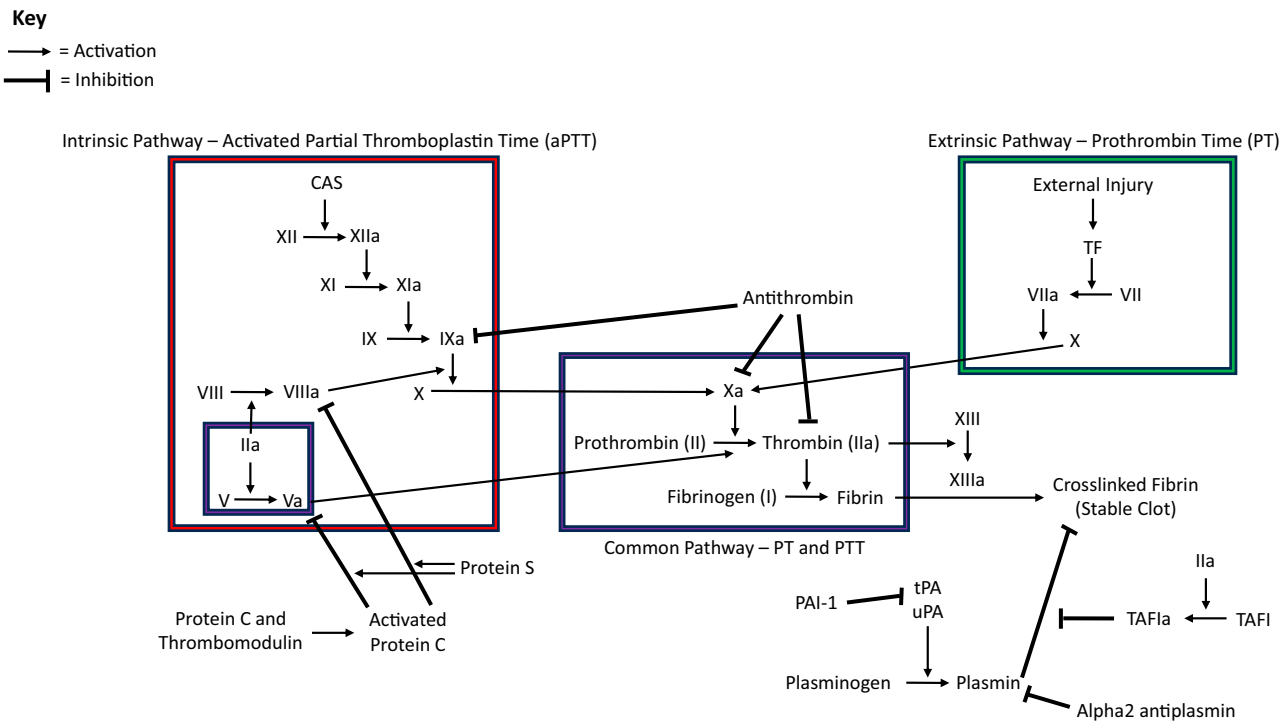

Figure. The classic coagulation cascade. The intrinsic pathway, which is tested by the aPTT, is encompassed in red, the extrinsic pathway, which is tested by the PT, is encompassed in green and the common pathway, which affects both PT and aPTT, is encompassed in purple. aPTT=activated partial thromboplastin time, CAS=contact activation system, composed of prekallikrein, kallikrein, and high-molecular-weight kininogen, PAI-1=plasminogen activator inhibitor 1, PT=prothrombin time, PTT = partial thromboplastin time, TAFI=thrombin activatable fibrinolysis inhibitor, TF=tissue factor, tPA=tissue plasminogen activator, uPA=urokinase plasminogen activator.

inflammatory pathways with excessive thrombin generation. (64) Underlying conditions, including infection, trauma, or malignancy, trigger hemostatic processes and thrombin generation. Thrombin then leads to fibrin formation, involves the fibrinolytic pathway, and depletion of hemostatic factors (proteins C/S, antithrombin) causing small vessel thrombosis and organ dysfunction, significant bleeding, and capillary leak, resulting in third-spacing. (64) As DIC is caused by other underlying disease states, the definitive treatment is based on the underlying disorder. (65) Supportive care can be offered with transfusions, through modulating thrombin generation (heparin or low-molecular-weight heparin), and with antithrombin/anticoagulant factor concentrates.

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) may be caused by the mutual atypical activation of both type 1 lymphocytes (ie, natural killer and CD8 cells) and mononuclear phagocytes (ie, dendritic cells and macrophages). (66) It consists of a constellation of symptoms, and one must meet 5 of 8 criteria for diagnosis. (66) These criteria are both clinical, such as splenomegaly and fever and abnormal laboratory values such as cytopenias (≥2 lineages; hemoglobin <10 g/dL [100 g/L] in neonates, platelets $<100 \times 10^3/\mu L$ [100×10^9/L]), decreased natural killer cell function, triglycerides greater than 265 mg/dL (3 mmol/L), ferritin greater than 500 ng/mL (500 μg/L), fibrinogen less than 15,000 mg/dL (150 g/L), hemophagocytosis, and soluble IL-2R levels/CD25 levels greater than 2,400 U/mL. (66) Given that the result of many of these diagnostic tests take time, clinical judgment is critical. Because of the poor specificity and sensitivity, the hallmarks of hemophagocytosis are not required to make the diagnosis. Several genetic conditions predispose individuals to HLH, such as familial HLH, pigmentary disorders, and disorders that increase susceptibility to Epstein-Barr virus infection. (67) Management of HLH involves a combination of immunosuppressive and chemotherapy medications, along with biological agents, to suppress the cytokine storm and target activated T-cells and macrophages. (66)(67)

Liver Disease

Liver disease causes changes in all 3 phases of hemostasis (primary and secondary hemostasis and fibrinolysis). (68) Portal hypertension can cause congestive splenomegaly and sequestration, limiting the number of circulating platelets. (68) Impairment in hepatic synthesis of thrombopoietin, which acts as the main regulator of platelet generation, leads

to dysregulation of platelet production. (68) The hepatic parenchymal cells produce all the necessary factors except for FVIII, which is produced by endothelial cells, making the reduced production of many factors (II, V, VII, IX, XI, and XIII) a hallmark of liver disease. (68) Conversely, the liver synthesizes all profibrinolytic and antifibrinolytic proteins, except for tissue plasminogen activator and PAI-1, which are produced by endothelial cells. (68) The homeostasis between bleeding and clotting is therefore even more precarious, and predicting whether a patient will bleed or develop thrombosis is challenging.

Vascular Anomalies

Vascular anomalies encompass a wide range of disorders marked by atypical development of lymphatic, arterial, venous, and capillary vessels. In vascular tumors, there is an abnormal increase in endothelial cell proliferation, whereas malformations primarily involve normal endothelial cells but display abnormal vessel arrangements. (69)

Kaposiform hemangioendothelioma (KHE) and tufted angiomas (TA) are benign vascular tumors commonly observed in infancy. KHEs tend to be more locally aggressive and burrow into deeper structures, whereas TAs tend to be more superficial (dermis and subcutis). (69) Kasabach-Merritt phenomenon (KMP) occurs in roughly 70% of patients with KHE and 10% to 20% of those with TA. (69) KMP is characterized by thrombocytopenia, low fibrinogen levels, increased D-dimer, and prolonged PT and aPTT. This is likely caused by platelet entrapment within the abnormal blood vessels of the tumor, leading to the depletion of platelets and coagulation factors. (69)(70) KMP lesions are red/deep purple, warm, tense, and painful. Treatment is complete resection if able or with sirolimus, oral steroids, and vincristine. (70)

Kaposiform lymphangiomatosis is similar to KHE/TA but involves lymphatic vasculature and is mainly found in the soft tissues, bones, spleen, and thoracic cavity. (71) Kaposiform lymphangiomatosis typically is severe, presents early in life, and displays progression. (70)(71) Coagulopathy is akin to KMP and is treated similarly. (71)

Summary

Coagulation disorders in infants can be challenging to diagnose given the physiologic differences in newborns and susceptibility to pregnancy conditions. When concerned about a coagulopathic condition, clinicians should be aware that:

- A comprehensive family and pregnancy history and physical examination can aid in identifying the cause of newborn coagulopathy.
- Initial laboratory screening should include a complete blood cell count with differential, PT, aPTT, and fibrinogen, with additional studies as clinically indicated. Abnormalities in the platelet count, PT, and aPTT will be beneficial in identifying the most common coagulopathic conditions, though there are severe bleeding disorders in which these laboratory findings are normal.
- Hematology consultation can be beneficial in assisting with diagnostic evaluation and management.

American Board of Pediatrics Neonatal-Perinatal 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.
- Know the inheritance patterns of the common coagulation factor deficiencies.
- Know the causes and pathophysiology of acquired defects in hemostasis.
- Know the clinical and laboratory features and management of acquired defects in hemostasis including intravascular coagulation and hemorrhagic disease of the newborn.
- Know the causes and pathophysiology of congenital defects in hemostasis.
- Know the clinical manifestations, laboratory findings, and management of congenital defects in hemostasis.

References

1. Broos K, Feys HB, De Meyer SF, Vanhoorelbeke K, Deckmyn H. Platelets at work in primary hemostasis. *Blood Rev*. 2011;25(4):155–167
2. Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood Rev*. 2015;29(1):17–24
3. Gale AJ. Current understanding of hemostasis. *Toxicol Pathol*. 2011;39(1):273–280

4. Smith SA, Travers RJ, Morrissey JH. How it all starts: Initiation of the clotting cascade. *Crit Rev Biochem Mol Biol*. 2015;50(4):326–336
5. Furie B. Pathogenesis of thrombosis. *Hematology Am Soc Hematol Educ Program*. 2009;2009(1):255–258
6. Winter WE, Flax SD, Harris NS. Coagulation testing in the Core Laboratory. *Laboratory Med*. 2017;48(4):295–313
7. Wu Y. Contact pathway of coagulation and inflammation. *Thromb J*. 2015;13:17
8. Caen J, Wu Q. Hageman factor, platelets and polyphosphates: early history and recent connection. *J Thromb Haemost*. 2010;8(8):1670–1674
9. Campbell SE, Bolton-Maggs PHB. Congenital and acquired bleeding disorders in infancy. *Early Hum Dev*. 2015;91(11):637–642
10. Kenet G, Chan AKC, Soucie JM, Kulkarni R. Bleeding disorders in neonates. *Haemophilia*. 2010;16(suppl 5):168–175
11. Venkatesh V, Curley A, Khan R, et al. A novel approach to standardised recording of bleeding in a high risk neonatal population. *Arch Dis Child Fetal Neonatal Ed*. 2013;98(3):F260–263
12. Poryo M, Boeckh JC, Gortner L, et al. PROGRESS study consortium and NGFN - Nationales Genomforschungsnetz Deutschland. Ante-, peri- and postnatal factors associated with intraventricular hemorrhage in very premature infants. *Early Hum Dev*. 2018;116:1–8
13. Kühne T, Imbach P. Neonatal platelet physiology and pathophysiology. *Eur J Pediatr*. 1998;157(2):87–94
14. Wasiluk A, Mantur M, Kemona H, Szczepański M, Jasińska E, Milewski R. Thrombopoiesis in small for gestational age newborns. *Platelets*. 2009;20(7):520–524
15. Saxonhouse MA, Sola-Visner MC. Thrombocytopenia in the neonatal intensive care unit. *Neoreviews*. 2009;10(9):e435–e445
16. Sola-Visner M. Platelets in the neonatal period: developmental differences in platelet production, function, and hemostasis and the potential impact of therapies. *Hematology Am Soc Hematol Educ Program*. 2012;2012:506–511
17. Murray NA, Roberts IA. Circulating megakaryocytes and their progenitors in early thrombocytopenia in preterm neonates. *Pediatr Res*. 1996;40(1):112–119
18. Ferrer-Marin F, Liu ZJ, Gutti R, Sola-Visner M. Neonatal thrombocytopenia and megakaryocytopoiesis. *Semin Hematol*. 2010;47(3):281–288
19. Sciscione AC, Bessos H, Callan N, Blakemore K, Kickler T. Indicators of platelet turnover in thrombocytopenic infants. *Br J Obstet Gynaecol*. 1997;104(6):743–745
20. Salama A. Alloimmune thrombocytopenias. *J Pediatr Hematol Oncol*. 2003;25 Suppl 1:S39–41
21. Kjeldsen-Kragh J, Killie MK, Tomter G, et al. A screening and intervention program aimed to reduce mortality and serious morbidity associated with severe neonatal alloimmune thrombocytopenia. *Blood*. 2007;110(3):833–839
22. Ferro M, Macher HC, Fornés G, et al. Noninvasive prenatal diagnosis by cell-free DNA screening for fetomaternal HPA-1a platelet incompatibility. *Transfusion (Paris.)*. 2018;58(10):2272–2279
23. Donato H. Neonatal thrombocytopenia: A review. I. Definitions, differential diagnosis, causes, immune thrombocytopenia. *Arch Argent Pediatr*. 2021;119(3):e202–e214
24. Norton T, Newberry D, Jnah A. Neonatal alloimmune thrombocytopenia: a concise review. *Adv Neonatal Care*. 2021;21(2):115–121
25. Bertrand G, Kaplan C. How do we treat fetal and neonatal alloimmune thrombocytopenia? *Transfusion (Paris)*. 2014;54(7):1698–1703
26. Gleason CA, Juul SE. *Avery's Diseases of the Newborn*. Tenth Edition; 2017
27. Yamamoto AY, Mussi-Pinhata MM, Marin LJ, Brito RM, Oliveira PFC, Coelho TB. Is saliva as reliable as urine for detection of cytomegalovirus DNA for neonatal screening of congenital CMV infection? *J Clin Virol*. 2006;36(3):228–230
28. Rawlinson WD, Boppana SB, Fowler KB, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis*. 2017;17(6):e177–e188
29. Hampton MM. Congenital toxoplasmosis: a review. *Neonatal Netw*. 2015;34(5):274–278
30. Carellos EVM, de Andrade JQ, Romanelli RMC, et al. UFMG Congenital Toxoplasmosis Brazilian Group (UFMG-CTBG). High frequency of bone marrow depression during congenital toxoplasmosis therapy in a cohort of children identified by neonatal screening in Minas Gerais, Brazil. *Pediatr Infect Dis J*. 2017;36(12):1169–1176
31. Gudeloglu E, Akillioglu M, Bedir Demirdag T, Unal NA, Tapisiz AA. Congenital rubella syndrome: a short report and literature review. *Trop Doct*. 2023;53(1):171–175
32. Zinkham WH, Medearis DN, Osborn JE. Blood and bone-marrow findings incongenital rubella. *J Pediatr*. 1967;71(4):512–524
33. Golemba MD, Mecikovsky D, Ortíz de Zárate M, et al. Unraveling HIV-1 diagnosis in special pediatric cases. *J Clin Virol*. 2020;131:104343
34. Diaz C, Hanson C, Cooper ER, et al. Disease progression in a cohort of infants with vertically acquired HIV infection observed from birth: the Women and Infants Transmission Study (WITS). *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;18(3):221–228
35. Fernandes ND, Arya K, Ward R. Congenital Herpes Simplex. In: *StatPearls*. StatPearls Publishing; 2024. Accessed March 17, 2024. http://www.ncbi.nlm.nih.gov/books/NBK507897/
36. Yang J, Zhang H, Niu J, et al. Impact of preeclampsia on megakaryocytopoesis and platelet homeostasis of preterm infants. *Platelets*. 2016;27(2):123–127
37. Martin RJ, Fanaroff AA, Walsh MC. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 11th ed. Philadelphia, PA: Elsevier; 2019.
38. Cowan J, Parikh T, Waghela R, et al. Thrombocytopenia with absent radii (TAR) syndrome without significant thrombocytopenia. *Cureus*. 2020;12(9):e10557
39. Tirthani E, Said MS, De Jesus O. Amegakaryocytic Thrombocytopenia. In: StatPearls. StatPearls Publishing; 2024. Accessed March 13, 2024. http://www.ncbi.nlm.nih.gov/books/NBK568795/
40. Al-Qahtani FS. Congenital amegakaryocytic thrombocytopenia: a brief review of the literature. *Clin Med Insights Pathol*. 2010;3:25–30
41. Cancio M, Hebert K, Kim S, et al. Outcomes in hematopoietic stem cell transplantation for congenital amegakaryocytic thrombocytopenia. *Transplant Cell Ther*. 2022;28(2):101.e1-101–e6
42. Malik MA, Masab M. Wiskott-Aldrich Syndrome - StatPearls - NCBI Bookshelf. Accessed March 13, 2024. https://www.ncbi.nlm.nih.gov/books/NBK539838/
43. Almomani MH, Mangla A. Bernard-Soulier Syndrome. *In:* StatPearls. StatPearls Publishing; 2024. Accessed March 13, 2024. http://www.ncbi.nlm.nih.gov/books/NBK557671/

44. Gunay-Aygun M, Zivony-Elboum Y, Gumruk F, et al. Gray platelet syndrome: natural history of a large patient cohort and locus assignment to chromosome 3p. *Blood*. 2010;116(23):4990–5001
45. Introne WJ, Huizing M, Malicdan MCV, O'Brien KJ, Gahl WA, et al. Hermansky-Pudlak Syndrome. In: Adam MP, Feldman J, Mirzaa GM eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed March 13, 2024. http://www.ncbi.nlm.nih.gov/books/NBK1287/
46. Echahdi H, El Hasbaoui B, El Khorassani M, Agadr A, Khattab M. Von Willebrand's disease: case report and review of literature. *Pan Afr Med J*. 2017;27:147
47. Eikenboom JC. Congenital von Willebrand disease type 3: clinical manifestations, pathophysiology and molecular biology. *Best Pract Res Clin Haematol*. 2001;14(2):365–379
48. Scully M. Congenital TTP: next stop, acuity and therapy. *Blood*. 2021;137(25):3469–3471
49. Gatseva A, Sin YY, Brezzo G, Van Agtmael T. Basement membrane collagens and disease mechanisms. *Essays Biochem*. 2019;63(3):297–312
50. Key NS, DE Paepe A, Malfait F, Shovlin CL. Vascular haemostasis. *Haemophilia*. 2010;16 Suppl 5:146–151
51. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet*. 2000;91(1):66–67
52. Soucie JM, Evatt B, Jackson D, The Hemophilia Surveillance System Project Investigators. Occurrence of hemophilia in the United States. *Am J Hematol*. 1998;59(4):288–294
53. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. *Lancet*. 2016;388(10040):187–197
54. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia panelists and co-authors. WFH Guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1–158
55. Pelcovits A, Schiffman F, Niroula R. Factor XIII deficiency: A review of clinical presentation and management. *Hematol Oncol Clin North Am*. 2021;35(6):1171–1180
56. Hsieh L, Nugent D. Factor XIII deficiency. *Haemophilia*. 2008;14(6):1190–1200
57. Karimi M, Peyvandi F, Naderi M, Shapiro A. Factor XIII deficiency diagnosis: Challenges and tools. *Int J Laboratory Hematol*. 2018;40(1):3–11
58. Hand I, Noble L, Abrams SA. Vitamin K and the newborn infant. *Pediatrics*. 2022;149(3):e2021056036
59. Committee on Nutrition. Report of Committee on Nutrition: vitamin K compounds and the water-soluble analogues. *Pediatrics*. 1961;28(3):501–507
60. Araki S, Shirahata A. Vitamin K deficiency bleeding in infancy. *Nutrients*. 2020;12(3):780
61. Mohsenian S, Palla R, Menegatti M, et al. Congenital fibrinogen disorders: a retrospective clinical and genetic analysis of the Prospective Rare Bleeding Disorders Database. *Blood Adv*. 2024;8(6):1392–1404
62. Fay WP, Parker AC, Condrey LR, Shapiro AD. Human plasminogen activator inhibitor-1 (PAI-1) deficiency: characterization of a large kindred with a null mutation in the PAI-1 gene. *Blood*. 1997;90(1):204–208
63. Carpenter SL, Mathew P. α2-Antiplasmin and its deficiency: fibrinolysis out of balance. *Haemophilia*. 2008;14(6):1250–1254
64. Toh CH, Alhamdi Y. Current consideration and management of disseminated intravascular coagulation. *Hematology Am Soc Hematol Educ Program*. 2013;2013(1):286–291
65. Wada H, Thachil J, Di Nisio M, et al. The Scientific Standardization Committee on DIC of the International Society on Thrombosis Haemostasis. Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. *J Thromb Haemost*. 2013 Published online February 4
66. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124–131
67. Canna SW, Marsh RA. Pediatric hemophagocytic lymphohistiocytosis. *Blood*. 2020;135(16):1332–1343
68. Kujovich JL. Coagulopathy in liver disease: a balancing act. *Hematology Am Soc Hematol Educ Program*. 2015;2015(1):243–249
69. Ricci KW, Brandão LR. Coagulation issues in vascular anomalies. *Semin Pediatr Surg*. 2020;29(5):150966
70. Adams DM, Brandão LR, Peterman CM, et al. Vascular anomaly cases for the pediatric hematologist oncologists—An interdisciplinary review. *Pediatr Blood Cancer*. 2018;65(1):e26716
71. Croteau SE, Kozakewich HPW, Perez-Atayde AR, et al. Kaposiform lymphangiomatosis: a distinct aggressive lymphatic anomaly. *J Pediatr*. 2014;164(2):383–388

NEO QUIZ

1. Coagulation factors are developmentally regulated and neonates, particularly those born preterm, are at increased risk of bleeding. While multiple coagulation factor levels are decreased in neonates, some are within normal range or increased. Which of the following coagulation factors is increased in neonates compared to adults and children?

   A. Factor II.
   B. Von Willebrand factor.
   C. Factor VIII.
   D. Protein C.
   E. Antithrombin.

2. Coagulation disorders are classified as disorders of primary hemostasis, disorders of secondary hemostasis, or disorders of the fibrinolytic system. Neonatal alloimmune thrombocytopenia (NAIT) is a disorder of primary hemostasis caused by the transplacental transfer of platelet-specific antibodies or human leukocyte antigen antibodies. NAIT occurs in approximately 1 in 1,000 births and presents with thrombocytopenia within 48 hours of birth. NAIT is an important diagnosis that must not be missed because subsequent pregnancies will need to be closely monitored for recurrence. What is the projected risk of NAIT recurrence in a subsequent pregnancy?

   A. 40%.
   B. 50%.
   C. 60%.
   D. 70%.
   E. 80%.

3. A term male neonate has prolonged bleeding after a circumcision. He was born after an uncomplicated pregnancy via cesarean section for breech presentation. He received 1 dose of intramuscular vitamin K at birth. His laboratory evaluation reveals a prolonged activated partial thrombin time (aPTT) with normal prothrombin time (PT) and platelet count. Which of the following diagnoses is most consistent with this clinical presentation?

   A. Factor VIII deficiency.
   B. Von Willebrand disease.
   C. Bernard-Soulier syndrome.
   D. Glanzmann thrombasthenia.
   E. Factor XIII deficiency.

4. A 3-day-old exclusively breastfed neonate born at 41 weeks' gestation develops irritability and altered mental status. He was born at home via uncomplicated vaginal delivery after an uncomplicated pregnancy. Brain imaging reveals the presence of an intracranial hemorrhage and you suspect classic vitamin K deficiency bleeding disorder (VKDB). Which of the following statements regarding VKDB is CORRECT?

   A. Classic VKDB presents between 3 and 21 days after birth.
   B. The presence of prolonged aPTT and normal PT on laboratory evaluations is consistent with the diagnosis of VKDB.
   C. Correction of coagulation test abnormalities within 2 to 6 hours of vitamin K administration helps confirm the diagnosis.
   D. Classic VKDB more commonly occurs in males and during the winter months.
   E. Late VKDB is characterized by spontaneous muscle hemorrhage, particularly of the lower extremities.

REQUIREMENTS: Learners can take *NeoReviews* quizzes and claim credit online only at: https://publications.aap.org/neoreviews.

To successfully complete 2024 *NeoReviews* articles for *AMA PRA Category 1 Credit*™, learners must demonstrate a minimum performance level of 60% or higher on this assessment. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2026, however, credit will be recorded in the year in which the learner completes the quiz.

2024 *NeoReviews* is approved for a total of 10 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics (ABP) through the AAP MOC Portfolio Program. *NeoReviews* subscribers can claim up to 10 ABP MOC Part 2 points upon passing 10 quizzes (and claiming full credit for each quiz) per year. Subscribers can start claiming MOC credits as early as October 2024. To learn how to claim MOC points, go to: https://publications.aap.org/journals/pages/moc-credit.

5. Liver disease can be associated with abnormalities in all 3 phases of hemostasis including primary and secondary hemostasis as well as fibrinolysis. All of the following factors are produced by the liver EXCEPT:

   A. Factor XIII.
   B. Factor VII.
   C. Factor II.
   D. Factor VIII.
   E. Factor IX.