Thrombotic Disorders in the Newborn

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EDUCATION GAP

Thrombus formation is common in neonates and can arise from both congenital and acquired causes, ranging from genetic abnormalities to indwelling catheters. Given this, neonatologists need to be able to identify when a thrombus is provoked, or when additional work is required, and how best to treat it.

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

1. Recognize which common coagulation abnormalities correspond to patterns of laboratory tests.
2. Recognize the common congenital conditions that place infants at risk for venous thromboembolism.
3. Identify the risk factors for an acquired venous thromboembolism.

ABSTRACT

The coagulation and thrombotic systems of an infant are fundamentally different from those of adults and older children. Hemostatic factors have inherently lower circulation levels in infants and are also affected prenatally by conditions of pregnancy. The unique physiology of neonates can contribute to a procoagulant state, which can result in a high level of morbidity and mortality. This review outlines the epidemiology, clinical characteristics, diagnosis and management, and etiologies of congenital and acquired forms of thrombotic disorders, with a discussion of the evaluation for hypercoagulation.

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ABBREVIATIONS

aPL	antiphospholipid
aPTT	activated partial thromboplastin time
AT	antithrombin
CVL	central venous line
DVT	deep vein thrombosis
LMWH	low molecular weight heparin
PT	prothrombin time
UAC	umbilical artery catheter
UFH	unfractionated heparin
UVC	umbilical vein catheter
VTE	venous thromboembolism

The coagulation system involves a careful biological balancing act between coagulation and thrombosis, with a visual representation of the coagulation cascade and the main pathways involved (Fig 1). (1) The figure shows the pathways and associated coagulation tests that clinicians can use to assist in identifying a coagulopathy or a procoagulant state. Primary and secondary hemostasis involve platelet aggregation and insoluble fibrin deposition, respectively, which in turn leads to a mature thrombus at the site of an injury or in response to an insult. (2)(3)(4) A disruption in these pathways can lead to a procoagulant state, in which hemostasis is shifted toward coagulation and thrombus formation, and

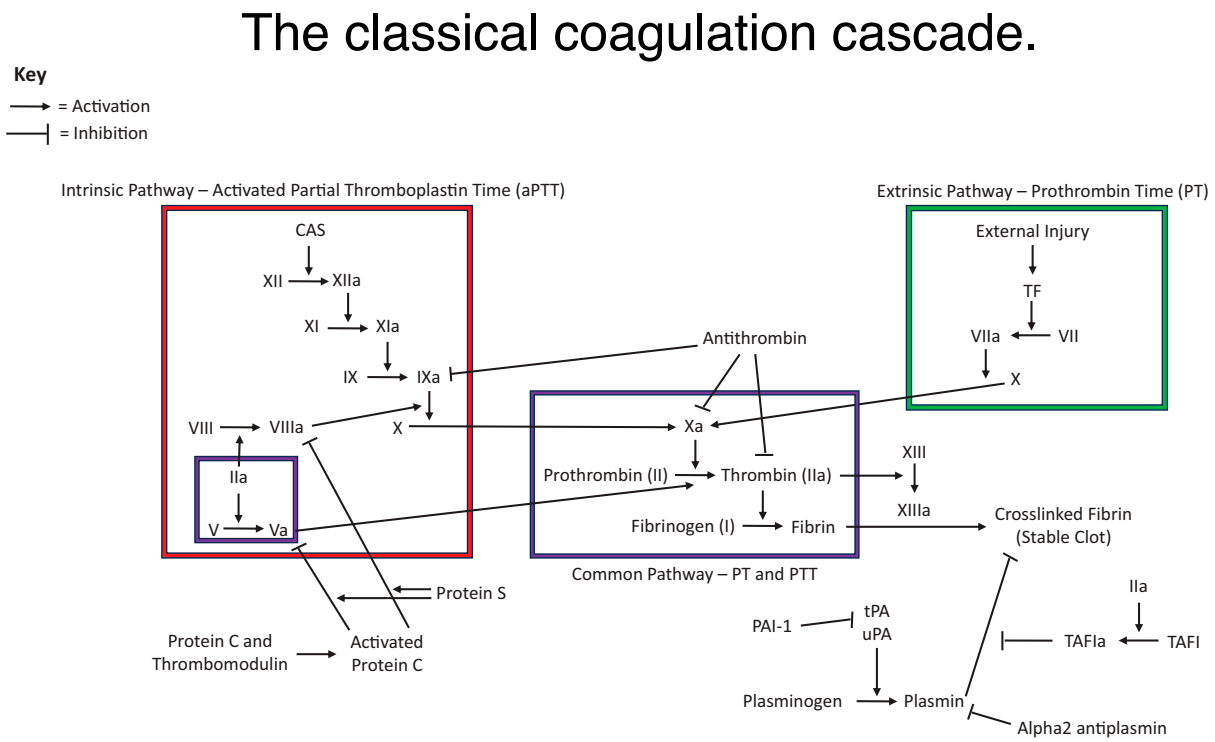

Figure 1. The classic coagulation cascade. The intrinsic pathway, which is tested by the aPTT, is encompassed in red; the extrinsic pathway, which is tested by the PT, is encompassed in green; and the common pathway, which affects both PT and aPTT, is encompassed in purple. aPTT=activated partial thromboplastin 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. (Reprinted with permission from Ostilla L, Knopoff K, Myers P, Morocco P. Disorders of coagulation in the newborn. NeoReviews. 2024;25(11):e694.

arise via either a congenital or an acquired cause, such as a line-associated deep vein thrombosis (DVT).

HEMOSTASIS OVERVIEW

The first step in thrombosis involves primary hemostasis, in which platelets bind to the exposed matrix of collagen and von Willebrand factor at sites of vessel injury. (2) These platelets are then activated, causing aggregation and the initial platelet plug, which combines with insoluble fibrin generated by secondary hemostasis, or the coagulation cascade (Fig 2). (2)(4)(5)(6) These steps lead to a stable thrombus, which is resistant to degradation. The 2 main pathways of secondary hemostasis, intrinsic and extrinsic, converge on the common pathway, and are represented by the prothrombin test (PT; encompasses extrinsic and common pathway) and the activated partial thromboplastin time (aPTT; encompasses the intrinsic and common pathway). (7) Once the thrombus is formed, the fibrinolytic system works to eventually dissolve the thrombus after the vessel endothelium has recovered from its injury. (3)

The body contains its own natural anticoagulants in the form of protein C, protein S, and antithrombin (AT), among others. These proteins exist on the other end of the coagulation cascade, working to block thrombus formation. Protein C and protein S are vitamin K–dependent glycoproteins that work to inactivate activated factor V and

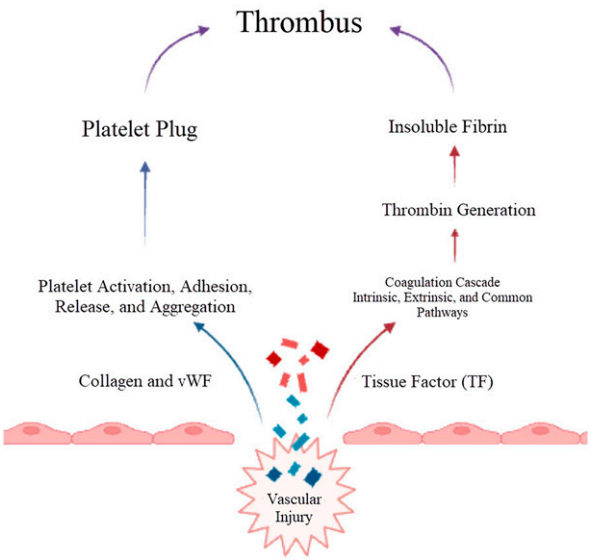

Figure 2. Overview of the infant's response to vascular injury.

Table. Overview, Management, and Key Points for Thrombotic Disorders in Infants

DISEASE/DISORDER	TAKE HOME POINTS	MANAGEMENT, IF APPLICABLE
AT deficiency	Autosomal dominant Venous and/or arterial thrombosis resistant to heparin treatment Diagnosis made through qualitative functional AT assays	Factor Xa inhibitors AT replacement
Protein C/S deficiency	Autosomal dominant Disseminated intravascular coagulation and neonatal purpura fulminans shortly after birth if homozygous or compound heterozygous Diagnosis by plasma levels or functional assays	Protein C replacement (FFP or Protein C concentrate) Protein S treated with anticoagulation
Factor V Leiden	Autosomal recessive The most common genetic risk factor for thrombosis Diagnosis by activated protein C resistance and direct gene analysis testing	
Prothrombin G20210A mutation	Arterial thrombus and central nervous system thrombosis seen in children <2yo	
Thrombocytosis	Primary–genetic mutation induces megakaryocytic hyperplasia; rare Secondary – infection, inflammation, anemia; related to thrombopoietin produced by the liver in times of stress	Secondary – benign, usually resolves spontaneously
Indwelling catheters	Most common cause of acquired thrombosis in neonates Higher risk with larger lumens, multiple lumens, femoral insertion sites, and temporary lines (peripherally inserted central catheter > port)	Short-term anticoagulation prior to line removal, treatment course varying from 6 wk – 3 mo with repeat imaging
Nephrotic syndrome	Hypercoagulability related to hypovolemia and hemoconcentration Urinary loss of anti-thrombotic proteins and increased platelet activation	Anticoagulation (LMWH) for thrombus and future prophylactic anticoagulation during flares
Antiphospholipid syndrome	Antibody-mediated hypercoagulability Venous and arterial thrombosis Confirmatory testing done 12 wk after suspicion/outside of illness Prolonged PTT without bleeding symptoms and does not correct with mixing study Lupus anticoagulant stronger indicator of thrombotic potential	Anticoagulation for 3 mo or longer with ongoing risk factors

AT=antithrombin, FFP=fresh-frozen plasma, LMWH, low-molecular-weight heparin, PTT=partial thromboplastin time.

factor VIII. (3) AT is another important part of coagulation, a serine protease with the ability to inactivate factor IXa/Xa and thrombin (factor IIa). (4)

EPIDEMIOLOGY

Thrombus formation is relatively common in infants in the NICU with the Pediatric Health Information System reporting that neonates had the second highest rate of venous thromboembolism (VTE) in admitted pediatric patients, at 75 per 10,000 admissions in 2007, only behind adolescents. (8) This number has only increased since 2001, when there were only 44 per 10,000 admissions in infants less than 28 days old, likely because of increased survival among critically ill neonates and their increasing complexity. (8) In infants, an estimated 90% of thrombotic incidents are linked to the use of a venous or arterial access device, with an umbilical vein catheter (UVC) conferring a 12% to 21% risk of thrombosis and an umbilical artery catheter (UAC) a 12% to 35% risk. (9)(10)(11) Risk factors for UVC-associated thrombi include blood transfusions, malposition of the UVC, increased duration of catheter placement, maternal diabetes, sepsis, necrotizing enterocolitis, family history of thrombus, and congenital heart disease. (12)(13) UAC-associated thrombi are more likely to occur in premature infants, with increased duration of catheter placement, sepsis, and perinatal asphyxia. (13) However, thrombi can also develop in the absence of a UVC or UAC; renal vein thrombi are the most common type that accounts for about 10% of thrombotic events in the neonatal period. (9)(14)

EVALUATION FOR HYPERCOAGULATION

When there are concerns for a prothrombotic condition, hematology consultation is recommended to aid in diagnosis and management with an overview provided in the Table. The most important aspects of the initial diagnostic evaluation are family and personal history of thrombosis, thrombus type, and location, and whether the thrombus could be considered

provoked or unprovoked in the current clinical setting. Risk factors, such as those described later in this review, help guide the decision to a hypercoagulation evaluation for a congenital cause contributing to the thrombus. This initial laboratory testing typically includes evaluation for deficiency in AT, protein C, and protein S, along with factor V Leiden and prothrombin G20210A mutation analysis, and antiphospholipid antibodies, including lupus anticoagulant. (15) Additional testing of factor VIII levels, lipoprotein(a), and homocysteine can also be considered, because all of these may lead to a higher likelihood of thrombosis. (16)

CONGENITAL THROMBOTIC DISORDERS

AT Deficiency

AT deficiency has an autosomal dominant pattern of inheritance. (17) AT is an endogenous anticoagulant, and its shortage leads to the most severe type of thrombophilia, with a 300-fold increase in risk of VTE compared with the normal population. (17) AT functions to inhibit thrombin (factor IIa), activated factor X (Xa), factor IXa, and other serine proteases. (18) Symptoms include unexplained and recurrent venous and/or arterial thromboembolism, which are highly resistant to heparin treatment, DVT, pulmonary embolism, and other hypercoagulable events that can manifest after trauma, shock, sepsis, critical care admission, or surgical procedures. (19)

Diagnosis is difficult in the neonate as the mean AT-III levels in term newborns are 56% of those in the adult, and even lower in premature infants. (20) A thorough examination of family medical records along with quantitative laboratory functional tests can be conducted to help with diagnosis. Laboratory testing is done to assess plasma AT's capability to inhibit the chromogenic activity of exogenous factor IIa or factor Xa. (20)(21) These tests lack sensitivity to detect mild forms of the disease and formal diagnosis is made through qualitative functional AT assays that are best performed after recovery from clinical illness. (21) Treatment of symptomatic infants includes AT-III replacement, factor Xa inhibitors (such as rivaroxaban or apixaban), and AT replacement products in patients with severely low AT levels. (21)

Protein C and S Deficiency

Both protein C and protein S deficiencies are autosomal dominant conditions with varying degrees of penetrance. (22) If homozygous or compound heterozygous, both conditions will show symptoms of disseminated intravascular coagulation and neonatal purpura fulminans shortly after delivery. (22)(23) Other manifestations include retinal thrombosis, renal vein thrombosis, and cerebral vessel thrombosis, which can occur prenatally. (23) If the diagnosis is suspected, protein levels can be measured in the plasma or via functional assays. (23)(24) It is important to take into consideration that in preterm, small-for-gestational-age infants and infants of diabetic mothers, serum protein C levels are lower than those of adults. (25)

Management of affected infants includes protein C replacement therapy with plasma-derived viral inactivated protein C concentrate or fresh-frozen plasma if replacement is unavailable. Protein S deficiency is treated via anticoagulation. (22) In the event of purpura fulminans or large vessel thrombosis, unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) can be used with caution. (22)

Factor V Leiden

Factor V Leiden thrombophilia is an autosomal recessive condition leading to hypercoagulation and elevated thrombosis risk. It is the most common genetic risk factor for VTE and the homozygous mutation occurs in 1 in 5000 individuals of Caucasian origin where it is most common compared with other ethnic groups. (26)(27) The mutation is defined by an inadequate anticoagulant response to activated protein C and symptoms include recurrent and/or unprovoked DVT, pulmonary emboli, and Budd-Chiari syndrome. (26)(28) Budd-Chiari syndrome arises from a thrombosis causing blockage of the hepatic veins, and factor V Leiden testing should be sent on any neonate who presents with, or develops this condition. (29)

Diagnosis of factor V Leiden requires testing for activated protein C resistance as well as direct DNA analysis of the gene F5, which codes for factor V, to identify a mutation. Management depends on clinical manifestations and is treated according to standard guidelines with UFH or LMWH. (26)

Prothrombin G20210A Mutation

The prothrombin G20210A mutation is another well-described cause of thrombosis, and can result in arterial thrombosis and central nervous system thrombosis in children younger than 2 years. (30) With increased levels of prothrombin, about 133% of normal, this mutation contributes to thrombotic risk. (30)(31) Like factor V Leiden, the mutation is seen most commonly in white populations, in whom it is found in 3% to 17% of patients with VTE. (31) Although most patients are heterozygous carriers, in very rare instances a patient can be homozygous

for the mutation, which seems to increase the likelihood of thrombosis. (30)(32)

The mutation can cause venous or arterial thrombosis, but in patients younger than 2 years, arterial thrombosis is more common, especially in neonates. (30) In any neonate with an unprovoked arterial thrombus, or finding of a central nervous system thrombus, prothrombin gene analysis should be performed to evaluate for the mutation. (30)

THROMBOCYTOSIS

Thrombocytosis, or increased platelet production, can be defined as either a primary or secondary process with secondary (reactive) thrombocytosis being more common among infants. (33) Sick infants face an increased risk of complications due to thrombocytosis because of their inherently low AT, protein C, and protein S levels as well as the smaller diameter of their blood vessels. (30) A family history of thrombotic events should be evaluated in any infant with an unexplained thrombotic event.

Secondary thrombocytosis is a reactive process in which infection, inflammation, or anemia causes an increase in an infant's platelet production. Reactive thrombocytosis is more common among preterm infants, is generally benign, and resolves spontaneously. (34) Thrombopoietin is the growth factor responsible for platelet production and is produced primarily by the liver. During times of stress or infection, hepatic thrombopoietin increases in response to inflammatory interleukins, driving the reactive thrombocytosis commonly observed. (35)

Primary thrombocytosis is uncommon and arises from a genetic mutation that induces hyperplasia of megakaryocytes in the bone marrow. (36) Unlike reactive thrombocytosis, primary thrombocytosis can lead to arterial thrombosis and myocardial infarctions, though affected patients are typically asymptomatic. (35) Patients with chronic myeloproliferative neoplasm essential thrombocythemia present with an increased platelet count; this condition is extremely rare with a global incidence of 0.6 per 100,000 patients per year in pediatric patients. (37) Diagnosis is challenging and is based on the World Health Organization 2016 criteria that requires a combination of thrombocytosis (platelet count $\geq 450 \times 10^3/\mu L$ [$450 \times 10^9/L$]); bone marrow with megakaryocyte proliferation; a *JAK2*, *CALR*, or *MPL* gene mutation; and lack of criteria to diagnose chronic myeloid leukemia, other chronic myeloproliferative neoplasms (such as polycythemia vera), myelodysplastic syndromes, or a myeloid malignancy. (38) This must all occur in the absence of reactive thrombocytosis. (38) Pediatric patients with essential thrombocythemia may experience minor hemorrhage because of poor platelet function despite high circulating platelet counts, and have a low risk of thrombotic complications (4%). (35)(39)

ACQUIRED THROMBOTIC DISORDERS

Indwelling Catheters

Thrombosis associated with central venous lines (CVLs) is "classified into three types: pericatheter sheath, thrombotic occlusion of the catheter lumen, and mural thrombosis, either superficial or deep vein." (40) In neonates, these CVLs are in the form of UVCs/UACs, peripherally inserted central catheter lines, and Hickman catheters (eg, Broviacs).

Thromboses can begin forming within hours of line insertion due to venous injury activating coagulation cascades, fibrin deposition on foreign catheter material, and almost immediate regrowth of surrounding endothelial and smooth muscle cells. (40) Blood flow can be decreased up to 60% around lines, which disrupts laminar flow and then causes additional adhesion of coagulation factors and platelets around the catheter itself. (40) The risk for thromboses is greater in newborns compared with other populations because of their small vessel size and immaturity of their clotting mechanisms especially in the face of hemostatic imbalance caused by fluid status, congenital heart disease, or hypoxia. (41)

Known patient-related risk factors for line-associated clots are malignancy, previous history of thrombosis, and systemic infection. (9)(10)(11)(13)(40)(41) Risk factors associated with the line itself are related to type/lumen size, access location, and time from insertion. Higher risk is conveyed to larger diameter of the catheter, multilumen lines, temporary lines (peripherally inserted central catheters more than ports), and femoral insertion sites. (40) Long-term total parenteral nutrition as well as hyperosmolar solutions convey a higher risk of thrombosis due to catheter-induced occlusion of vessels and increased risk of endothelial vessel damage. (41)

Frequently, in neonates, UFH infusions are started alongside CVL insertion to allow infants to complete their needed treatments (antibiotics, parenteral nutrition, etc). However, these infusions do not decrease the rate of thrombosis but rather reduce occlusion. (41)

Although most thromboses related to catheter events are asymptomatic, clinical manifestations include edema (localized or including surrounding areas/drainage pathways), erythema, and pain/tenderness. The primary treatment approach involves anticoagulation, and the decision to remove the CVL is made on an individual basis. Short-term anticoagulation is recommended before line removal.

(41) Thromboses in an artery should prompt removal of the line and initiation of LMWH or UFH for at least 10 days. (41) Provoked VTEs are treated for 6 weeks to 3 months with anticoagulation and reimaged before discontinuing therapy to ensure that the thrombosis has completely resolved, or become chronic. (40) Goal anti–factor Xa levels of 0.5 to 1.0 IU/mL when using LMWH and 0.35 to 0.7 IU/mL if using UFH. Of note, neonates require higher doses of enoxaparin, in the range of 1.7 to 2.0 mg/kg every 23 hours, because of the lower levels of AT and large volume of distribution. (41)(42)

Nephrotic Syndrome

Patients diagnosed with nephrotic syndrome are at increased risk for thrombosis (2%–3%), particularly DVTs and renal vein thrombosis. (43) Hypercoagulability stems from thrombocytosis arising from hypovolemia and hemoconcentration; increased platelet activation; urinary losses of AT; deficiency of protein C, protein S, and plasminogen; and increased levels of fibrinogen and factors V and VIII caused by dysregulated compensatory protein synthesis. (43) Congenital nephrotic syndrome is rare and is most commonly found in infants of Finnish descent, with an incidence of 1 in 8,200 live births. (44)

Anticoagulation is usually initiated with LMWH in response to a thrombus, as it has more predictable pharmacokinetics and there is no need for intravenous access. (43) UFH can be used if there is a need for quick reversal or tight titration. (43) Anticoagulation at prophylactic doses should then be used when patients have flares of nephrotic syndrome, to prevent further thrombotic events. (45)

Antiphospholipid Syndrome

Antiphospholipid (aPL) syndrome is an antibody-mediated hypercoagulability with repeated venous and/or arterial thrombotic events, along with other hematologic manifestations, including thrombocytopenia and/or hemolytic anemia. (46) aPL antibodies are a diverse set of immunoglobulins targeting proteins that bind to phospholipids; common screening aPL assays include anticardiolipin antibody, anti-β2 glycoprotein, and lupus anticoagulant. (47) Because in some instances aPL syndrome can be a transient phenomenon in reaction to infection, underlying autoimmune disorders, medications, and/or malignancy, initial testing is done at the time of the event, and repeat confirmatory testing is completed 12 weeks or more later. (46) A prolonged aPTT in the absence of bleeding symptoms or a bleeding history could be from positive aPL antibodies, which can be confirmed if an aPTT mixing study does not appropriately correct. The presence of aPL antibodies alone is insufficient for the diagnosis of aPL syndrome, and patients with aPL antibodies require another insult, such as trauma or a congenital prothrombotic disorder, for thrombus formation to occur. (48) Primary aPL syndrome occurs without any associated disease, whereas secondary aPL syndrome is associated with another condition, such as systemic lupus erythematosus or another autoimmune condition. (48)

aPL antibodies bind and activate endothelial cells, neutrophils, and platelets, resulting in proinflammatory cytokines and complement activation. (48) They also interfere with anticoagulant pathways including fibrinolysis by inhibiting protein C and inhibiting β2GPI, which normally blocks factor Xa formation, thrombin activation, and platelet aggregation. (48) The summation of these effects results in a prothrombotic state, and an increased risk of stroke is seen more often in pediatric cases compared with adult cases, where there is typically an underlying autoimmune condition and more VTE events. (49) Lupus anticoagulant is the stronger indicator of thrombotic potential compared with anticardiolipin antibody, which does not appear to confer thrombotic risk, but triple-positive aPL syndrome has the highest risk. (47)(48) aPL syndrome in pregnant persons can result in the transfer of these antibodies to the fetus via the placenta, but this does not appear to result in perinatal thrombosis. (50)

After a thromboembolic event in the setting of positive aPL, anticoagulation is recommended for at least 3 months or longer if there is an ongoing risk factor. (45) If there are recurrent episodes of thromboembolism, anticoagulation is advised for as long as the risk factor is present. (45)

Summary

Thrombophilia is common in infants, especially neonates hospitalized in the NICU, which confers additional morbidity and mortality. Clinicians caring for such patients should be aware that:

- Hypercoagulability testing may not be indicated based on the clinical scenario surrounding the diagnosis of an acute thrombus.
- CVLs are the most common cause of thrombosis in neonates, but congenital and other acquired prothrombotic states contribute to a small subset of arterial or venous thromboembolism.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and pathophysiology of congenital and acquired thrombotic disorders.
- Know the clinical and laboratory features, management, and potential adverse effects of treatment of congenital and acquired thrombotic disorders.
- 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.
- Know the pathogenesis and complications of catheter-related thrombi including umbilical arterial and central venous catheters.

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NEO QUIZ

1. An infant of 31 weeks' gestation requires long-term venous access for medication administration and fluid management. After the placement of an umbilical venous catheter, there appears to be prolonged blood oozing at the insertion site. The team suspects a defect in hemostasis. Of the 2 main pathways of secondary hemostasis, testing which of the following would demonstrate a defect in the intrinsic pathway?

   A. Activated partial thromboplastin time (aPTT).
   B. Antithrombin III level.
   C. Bleeding time.
   D. Platelet count.
   E. Prothrombin time.

2. Three weeks after admission to the NICU for management of prematurity, a former 29-weeks gestation infant is found to have a thrombotic incident. Of the following, which is most likely to be linked to this event?

   A. Blood transfusions.
   B. Chorioamnionitis.
   C. Respiratory distress syndrome.
   D. Sepsis.
   E. Venous or arterial access devices.

3. Shortly after delivery, a term infant develops diffuse bruising. On further investigation, the neonate demonstrates signs of disseminated intravascular coagulation and is found to have retinal thrombosis on ophthalmologic examination. Of the following, which condition most likely contributed to these findings?

   A. Antiphospholipid syndrome.
   B. Antithrombin deficiency.
   C. Factor V Leiden.
   D. Protein C and S deficiency.
   E. Prothrombin G20210A mutation.

4. Unlike secondary thrombocytosis, which can be caused by infection, inflammation, or anemia, primary thrombocytosis is a rare condition caused by genetic mutations in the *JAK2*, *CALR,* or *MPL* genes, leading to hyperplasia of megakaryocytes in the bone marrow and thrombocytosis. What platelet count is required to meet the diagnostic criteria of primary thrombocytosis?

   A. $\geq 150 \times 10^9$/L.
   B. $\geq 300 \times 10^9$/L.
   C. $\geq 450 \times 10^9$/L.
   D. $\geq 600 \times 10^9$/L.
   E. $\geq 750 \times 10^9$/L.

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5. Nephrotic syndrome places an infant at increased risk for thrombosis (particularly renal and deep vein thrombosis). This hypercoagulable state stems from thrombocytosis due to hypovolemia and an increase of all of the following except:

   A. Factor V.
   B. Factor VII.
   C. Fibrinogen.
   D. Plasminogen.
   E. Platelet activation.