Pediatric Coagulation Disorders

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Practice Gap

Clinicians are often challenged in primary practice with patients who present with potential hemostatic disorders. Determining which laboratory tests to order and when to refer a patient to a pediatric hematologist is of vital importance.

Objectives  After completing this article, the reader should be able to:

1. Describe the physiology of hemostasis in the pediatric patient.
2. List clinical signs and symptoms suggestive of a congenital or acquired bleeding disorder.
3. Understand laboratory testing and indications in the diagnosis of a bleeding disorder and timing of subspecialty referral.
4. Describe the clinical management of bleeding disorders.
5. Become familiar with congenital and acquired thrombophilic disorders and their diagnosis and management recommendations.

INTRODUCTION

Hemostasis in the pediatric patient evolves as the child grows and matures, and normal adult laboratory values are not often the norm for a child. This article provides a summary of the pathophysiology of hemostasis (eg, bleeding and thrombosis disorders) and reviews the basic principles of history and physical findings to provide the primary care practitioner with the necessary tools for initial evaluation of a pediatric patient with a suspected coagulation disorder. A basic understanding of when to test a patient for a coagulation disorder or make a proper referral to a pediatric hematologist will result in optimal care.

PATHOPHYSIOLOGY OF HEMOSTASIS

Hemostasis is a complex process that requires a balance between maintaining blood in a fluid state and addressing areas of tissue injury in which a local response is generated at the site of vascular endothelial injury to promote healing and prevent hemorrhage. This process requires the interaction of the vascular endothelium, platelets, and coagulation factors. Diminished or dysfunctional activity of any of the components of the hemostatic system leads to coagulopathy,
and different bleeding or thrombotic manifestations depend on the severity or lack of function of a particular hemostatic component.

The hemostatic process is initiated at the site of tissue or vascular injury. The disrupted vascular endothelial cells, exposed subendothelial connective tissue, and smooth muscle activate their procoagulant properties with the release of von Willebrand factor (vWF), which allows platelet binding (primary hemostasis). Platelets are anucleate discoid cells (normal size 0.5–3.0 μm) that contain granules with procoagulant factors and surface receptors that enable their attachment to the damaged endothelium. Three phases traditionally describe platelet activation: adhesion, activation, and aggregation. Through adhesion, platelets attach to the damaged endothelium with the help of cell surface receptors (mediated through glycoprotein [GP] Ib-IX-V receptor). Once attached to the endothelium, platelets are activated via intracellular signaling mechanisms, resulting in granule release. The released substances constitute chemotactic factors (adenosine diphosphate [ADP] and thromboxane A2) and cofactors for the intrinsic pathway of coagulation cascade and fibrin formation, leading to platelet aggregation (platelet interaction with vWF and platelet-to-platelet binding mediated by GPIIb-IIIa receptor, secondary hemostasis). Tissue factor binds to factor VII (FVII) (extrinsic pathway) and with the help of platelet-derived phospholipids, calcium, further activates factor X (FX) (Figure). FX interacts with factor V (FV), prothrombin, calcium, and phospholipids, ultimately generating thrombin. Thrombin can generate further thrombin through activation of the contact factor pathway (intrinsic pathway) via positive feedback.

The extrinsic and intrinsic pathways are descriptions of in vitro assays and how the original coagulation cascade was discovered rather than actual in vivo physiology. Both
pathways interact and provide several feedback loops to augment the activity or cause enzymatic activation of several of the coagulation components. Both pathways converge in the common pathway, with activation of FX resulting in the conversion of fibrinogen into fibrin, along with factor XIII (FXIII) activation that crosslinks fibrin for better clot stabilization (Figure).

Several anticoagulant proteins help maintain the blood in a fluid state by neutralizing the activity of thrombin, including antithrombin (AT), heparin cofactor II, and α-2 macroglobulin. Protein C, protein S, and thrombomodulin inactivate FV and factor VIII (FVIII) and by their function, inhibit thrombin generation. Eventually, fibrinolytic factor plasminogen, when activated to plasmin by plasminogen activators (tissue plasminogen activator, urokinase), acts on the fibrin clot to dissolve it and naturally regulate the coagulation process. Fibrinolysis is controlled by plasminogen activator inhibitors (PAIs) such as PAI-1 and plasmin inhibitors such as α2-antiplasmin. This dynamic and complex interplay of pro- and anticoagulants promotes hemostasis when needed and prevents abnormal generation of a fibrin clot in areas where there is no endothelial injury. Quantitative or qualitative abnormalities in the activity of procoagulant factors lead to bleeding disorders, while abnormalities in the function and activity of anticoagulant proteins result in an increased risk of thrombosis.

EVALUATION OF A BLEEDING DISORDER

History and Physical Examination

The best screening test for a bleeding disorder is a comprehensive history and physical examination. (1)(2)(3) The primary hindrance to finding such disorders is a lack of surgical challenges or trauma in the pediatric age group that can provide additional clues toward the diagnosis. Mild bleeding symptoms, such as epistaxis and easy bruising, are relatively common in children. The patient's age, gender, and developmental stage are important to consider when evaluating a possible bleeding disorder. The different components of the coagulation system are constantly evolving, and concentrations of coagulation proteins in the pediatric patient might not reach adult reference values until adolescence or adulthood. (4)(5)(6)(7) Easy bruising is a common finding in children between ages 1 and 10 years, more frequently over bony prominences such as the forehead, knees, and shins. Nonaccidental trauma is always a concern for any clinician involved in pediatric care and should be considered in children with unexplained or excessive bleeding symptoms. Any type of bleeding in a non-mobile child should be considered to be a bleeding disorder or a result of non-accidental trauma.

Factors to consider when evaluating a bleeding disorder are the age of the patient at the time of the first episode; the site, frequency, and extent of the bleeding; personal history of recurrent unprovoked or spontaneous bleeding; bleeding after surgical or procedural interventions; family history of bleeding; and heavy menstrual bleeding in girls. Bleeding symptoms from primary hemostatic defects such as abnormalities of platelets are characterized by easy bruising or petechiae, mucosal bleeding, and bleeding after trauma. Defects of secondary hemostasis such as coagulation factor deficiencies cause delayed bleeding after surgery, trauma, deep lacerations, and depending on the degree of coagulation factor deficiency, bleeding into joints, muscles, and soft tissues. During the neonatal period, oozing from the umbilical stump, prolonged oozing from heel stick or venipuncture sites, prolonged bleeding from circumcision, large cephalohematoma, and caput succedaneum without a traumatic birth history suggest a congenital bleeding disorder. Intracranial hemorrhage in a near-term or term neonate should raise concern about a potential congenital bleeding disorder.

Other medical disorders that can cause easy bruising or bleeding should be considered. Ehlers-Danlos syndrome is a disorder of collagen, and patients typically present with hyperextensible joints and easy/prominent ecchymosis. Hemangiomas and hereditary hemorrhagic telangiectasias are vascular disorders that can present with bleeding symptoms, particularly in the airway and gastrointestinal tract.

A detailed history of medications, nonprescription supplements, and complementary medications should be documented in the history. Some of these can cause acquired coagulation abnormalities, including aspirin, nonsteroidal anti-inflammatory drugs, and Ginkgo biloba extract.

Initial Laboratory Evaluation

The initial laboratory evaluation of a child with a suspected bleeding disorder should include a complete blood cell (CBC) count, peripheral blood smear, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, thrombin time, von Willebrand antigen and activity (vWF activity or ristocetin cofactor activity), FVIII, and factor IX (FIX). The CBC count and peripheral blood smear complement each other. They not only provide diagnostic evidence of quantitative platelet disorders but can also assist in the evaluation of white cell and platelet morphology that can offer clues toward the diagnosis of congenital platelet disorders (eg, Döhle bodies in white cells and large platelets in May-Hegglin anomaly) or confirm the diagnosis of a
malignant disorder such as leukemia. Morphologic evaluation of red cells can exclude disorders such as a microangiopathic process that can lead to fragmented red blood cells and thrombocytopenia (eg, hemolytic-uremic syndrome/thrombotic thrombocytopenia purpura).

Prolongation of PT and aPTT in an asymptomatic child may be due to several factors. A common cause of prolonged clotting times is error in obtaining an adequate amount of blood or delay in processing the blood samples. Lupus anticoagulants (LA) are often present in children after viral infections and can prolong phospholipid-dependent assays such as PT and aPTT without any bleeding consequences. LA cause thrombosis most commonly in patients with autoimmune disorder. In rare instances, LA can cause acquired prothrombin deficiency. Table 1 summarizes the differential diagnosis based on abnormalities of different coagulation assays.

Nonaccidental Trauma
If bleeding or bruising raises concern for nonaccidental trauma, careful history, physical examination, and detailed description of physical findings are warranted. Bruises in areas less prone to trauma, such as the face, ears, neck, upper arms, trunk, hands, genitalia, buttocks, and anterior and medial thighs, as well as the pattern of bruises (eg, hand marks, bite marks, object marks, bruises in clusters, or large cumulative bruises) should raise concern for child abuse. Laboratory evaluations need to be undertaken but with the understanding that the presence of a bleeding disorder or coagulation abnormality does not rule out abuse or nonaccidental trauma as an explanation for recurrent bruising or bleeding. If the history and physical findings disclose or provide a clear explanation for the easy bruising or bleeding, a bleeding disorder evaluation might not be needed. However, in the absence of a clear explanation or findings on physical examination such as petechiae or bruising in areas of pressure to the skin (eg, bruising on the chest in areas where infant’s seat fasteners-belts are applied or areas of clothing pressure), evaluation for a bleeding disorder should be considered. If the child presents with intracranial hemorrhage, a disseminated intravascular coagulation (DIC) panel (d-dimer and fibrinogen) in addition to the previously mentioned coagulation laboratory tests should be obtained. If any of these tests yield abnormal results, clinicians should consider further testing. A consultation with a pediatric hematologist can facilitate interpretation and management recommendations.

INHERITED BLEEDING DISORDERS
Incidence and Characteristics
Hemophilia A and B are X-linked recessive disorders characterized by deficiencies of coagulation FVIII and FIX, respectively. Hemophilia A affects 1 in 5,000 males and hemophilia B affects 1 in 30,000 males, with an equal ethnic distribution. Hemophilia C (FXI deficiency) affects both

<table>
<thead>
<tr>
<th>LABORATORY FINDING</th>
<th>DIFFERENTIAL DIAGNOSIS</th>
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<tbody>
<tr>
<td>PT abnormal, aPTT normal</td>
<td>FVII deficiency</td>
</tr>
<tr>
<td>aPTT abnormal, PT normal</td>
<td>FVII, FIX, FXI, FXII deficiency; high-molecular weight kinininogen, prekallikrein, or kallikrein deficiency; severe vWD; heparin effect</td>
</tr>
<tr>
<td>PT and aPTT abnormal</td>
<td>FI, FII, FV, combined FV/FVIII, or FX deficiency or vitamin K coagulation factor deficiency</td>
</tr>
<tr>
<td>No abnormalities in PT and aPTT</td>
<td>Consider FXII, FVIII, or FIX (mild deficiencies)*; fibrinolytic disorders (α-2 antiplasmin deficiency; plasminogen activator inhibitor deficiency); platelet function disorders</td>
</tr>
<tr>
<td>PT and aPTT prolonged with prolonged TT</td>
<td>Afibrinogenemia, dysfibrinogenemia, DIC, heparin effect</td>
</tr>
<tr>
<td>PT and aPTT prolonged with normal TT</td>
<td>Liver disease; vitamin K deficiency; FII, FV, FX deficiency; DIC; lupus anticoagulant; warfarin effect</td>
</tr>
<tr>
<td>Platelet count low</td>
<td>Idiopathic thrombocytopenic purpura, hereditary platelet disorder, bone marrow failure syndrome</td>
</tr>
<tr>
<td>Platelet function analysis (abnormal platelet function analysis)</td>
<td>vWD, platelet disorder (hereditary or acquired)</td>
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*Interlaboratory assay variation; refer to institutional clotting times assay sensitivities for lower limit of detection of factor activities.

aPTT=activated partial thromboplastin time, DIC=disseminated intravascular coagulation, F=factor, PT=prothrombin time, TT=thrombin time, vWD=von Willebrand disease.
genders and is typically more common in Ashkenazi Jews. Because about 30% of hemophilies can develop as spontaneous mutations, the lack of family history does not rule out this disorder. FVIII and FIX should be measured in any male infant with suspected hemophilia. FVIII concentrations are similar in infants and adults, but FIX concentrations are lower in newborns, rising to adult values after age 6 months. Mild-to-moderate hemophilia B cannot be diagnosed in the neonate and assessment of FIX must be repeated at or after age 6 months to confirm the diagnosis.

The severity of hemophilia is based upon the concentrations of FVIII and FIX. Severe hemophilia is characterized by a less than 1% plasma factor level. Bleeding episodes are frequent and often spontaneous in the absence of trauma. Spontaneous joint hemorrhages, also known as hemarthroses, are characteristic of this severe bleeding disorder. Moderate hemophilia (factor levels 1%–5%) typically presents with bleeding symptoms (hematomas, mucosal bleeding) after minor trauma; spontaneous bleeding such as hemarthrosis is not as frequent as in severe hemophilia unless precipitated by trauma. Mild hemophilia (factor levels 5%–40%) typically manifests bleeding symptoms with surgery or significant trauma.

Females can be symptomatic carriers of hemophilia. They can also present with hemophilia by inactivation of the normal X chromosome via lyonization, homozygous recessive hemophilia status, and Turner syndrome (45XO). Diagnosis of hemophilia requires a complete history and pedigree of the family, measurement of FVIII and FIX, and genetic testing [DNA analysis of FVIII [26 exons] and FIX [8 exons]]. Prenatal DNA-based diagnosis of hemophilia can be undertaken via chorionic villus sampling at 10 to 12 weeks of gestational age.

**Treatment**

Most of the care for patients with hemophilia is performed at home, which is why patient education and counseling constitute a substantial part of the management. Parents and older children are taught how to infuse factor concentrates intravenously. Some young children, particularly with severe hemophilia, require the use of central venous access devices (eg, implanted catheters) to facilitate factor infusion. The standard of care for patients with severe or moderate hemophilia who have recurrent bleeding episodes is prophylactic factor infusion to prevent spontaneous hemorrhages, especially into the joints. Hemarthrosis can cause degenerative joint disease that affects mobility and function. Hemophilia care also requires on-demand therapy (factor infusion to treat any acute bleeding) or infusion of factor before a physical activity or sport that can potentially lead to muscle or joint bleeding. The combination of these treatment strategies prevents degenerative joint disease, improves quality of life, and allows children to develop a healthy musculoskeletal system as they mature into young adults. Unfortunately, before the 1980s, many patients with hemophilia received their therapy with plasma-derived products and some developed human immunodeficiency virus or hepatitis B and C infections. With the advent of DNA recombinant factor products and purified factor concentrate technology, the viral transmission of these diseases was halted. New longer-acting products with longer half-lives are approved by the US Food and Drug Administration (FDA) and are available commercially, facilitating less frequent factor concentrate infusions compared to the traditional FVIII and IX concentrates.

Children who have severe hemophilia are not only at risk for repetitive bleeding into joints (“target joints”), pain, decreased range of motion, and degenerative joint disease, but they can also develop intracranial hemorrhage with trauma if factor therapy is not administered immediately. Moreover, these children can develop inhibitors (antibodies) that render coagulation factor concentrates ineffective. Therapy to eradicate these types of antibodies requires prolonged and higher doses of factor concentrates, also known as immune therapy. These antibodies are measured by the Bethesda assay. One Bethesda unit per milliliter inhibits or neutralizes FVIII or FIX by 50%. Children with severe disease require specialized care by a hematologist for comprehensive bleeding treatment management guidance. Patients who have inhibitors and acute hemorrhage require the use of FVIII or FIX bypassing agents (eg, recombinant FVII, prothrombin complex concentrates).

The goal of replacement therapy in those who have hemophilia during an acute bleeding episode is to raise the concentration of the involved plasma factor to the desired level for hemostasis based on the type and severity of the bleeding. Patients with minor hemorrhages or hemarthrosis can be treated with the goal of achieving at least 20% to 40% of FVIII or FIX activity (Table 2). More severe bleeding, such as intracranial hemorrhage, should be treated to correct the factor level to 100% activity (Table 2).

Patients with mild hemophilia A may respond to desmopressin (DDAVP; i-deamino-8-D-arginine vasopressin). DDAVP is a synthetic analog of arginine vasopressin that induces vWF and FVIII release from the endothelium. Minor bleeding or mucosal bleeding can be treated with this agent in patients who demonstrate response to therapy (elevation of FVIII and vWF from baseline). Mucosal bleeding can also be treated with antifibrinolytics such as tranexamic acid and ε-aminocaproic acid. Both medications...
inhibit the conversion of plasminogen to plasmin, thereby inhibiting lysis of a fibrin clot.

**VON WILLEBRAND DISEASE**

**Characteristics**

von Willebrand disease (vWD) is the most common bleeding disorder, affecting nearly 1% of the population. vWF is a plasma GP that is composed of low-, intermediate-, and high-molecular weight multimers. vWF binds to platelets through GPIb-IX-V and GPIIb-IIIa on the surface of the platelets, promoting platelet adhesion and aggregation, respectively, at the injured vascular endothelium. vWF also serves as a carrier for FVIII in the circulation.

The majority of vWD diagnoses are type 1 variant (nearly 80%), which involves a quantitative defect in vWF and is generally associated with mild bleeding symptoms. About 20% of vWD diagnoses are type 2. Type 2A vWD results from qualitative deficiency of large-molecular weight multimers, vWF binds to platelets through GP Ib-IX-V and GP IIb-IIIa on the surface of the platelets, promoting platelet adhesion and aggregation, respectively, at the injured vascular endothelium. vWF also serves as a carrier for FVIII in the circulation.

Type 2B vWD can be diagnosed by measuring low-dose ristocetin-induced platelet aggregation.

**Treatment**

Treatment depends on the type of vWD and bleeding severity. DDAVP is an option for those with type 1 and some type 2A vWD. A DDAVP “challenge” or infusion must be performed initially to measure the response after administration, assessed by an increase in FVIII, vWF antigen, and vWF activity or ristocetin cofactor activity. The dose of DDAVP is 0.3 µg/kg intravenously, with some recommending a maximum dose of 20 µg. A nasal form is also available, which is convenient to administer for minor bleeding or in emergency situations when patients do not have ready access to a medical facility. Both nasal and intravenous DDAVP can be administered every 12 to 24 hours, although caution should be exercised due to tachyphylaxis (decreased response if frequent and repetitive use) and the possibility of hyponatremia with potential risk for seizures, especially in infants and young children. Other adverse effects are headaches, facial flushing, and tachycardia, but these are transient. In females with vWD and menorrhagia, DDAVP in addition to antifibrinolytics can be used to control bleeding. Oral contraceptives/hormonal therapy also can be considered to control heavy menstrual periods.

**TABLE 2. Treatment Recommendations for Hemophilia A and B**

<table>
<thead>
<tr>
<th>TYPE OF BLEEDING</th>
<th>DESIRED PLASMA FACTOR LEVEL</th>
<th>INITIAL DOSE OF FVIII* (IU/KG)</th>
<th>INITIAL DOSE OF FIX* (IU/KG)</th>
<th>DURATION OF THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD: Hemarthrosis, superficial hematoma, oropharyngeal bleeding</td>
<td>20%-40%</td>
<td>20–30</td>
<td>20–40</td>
<td>1–2 days</td>
</tr>
<tr>
<td>MAJOR: Central nervous system trauma, surgery, gastrointestinal bleeding, retroperitoneal bleeding</td>
<td>80%-100% (for at least initial 72 hours; &gt;50% thereafter)</td>
<td>50</td>
<td>100</td>
<td>At least 10–14 days</td>
</tr>
</tbody>
</table>

*Each unit of FVIII per kilogram of weight infused increases the plasma factor level by 2% and each unit of FIX per kilogram of weight increases the plasma factor level by 1%. Slight variations can be encountered in the expected increment level of factor plasma activity level among the different commercially available products. FVIII=factor VIII, FIX=factor IX.
Therapy with DDAVP is contraindicated in other subtypes of type 2 vWD, such as type 2B due to worsening thrombocytopenia and type 3 due to lack of response related to near absence of vWF. Factor concentrates and antifibrinolytics are used to treat bleeding episodes. Several commercial brands of vWF concentrates, which contain a higher proportion of vWF, are designed specifically to treat these disorders.

### PLATELET DISORDERS

Congenital platelet disorders can affect platelet numbers, function, or both. The typical clinical manifestations are excessive mucocutaneous bleeding, such as easy bruising, palpable ecchymosis or purpura, excessive bleeding following surgical or dental procedures, or bleeding due to trauma.

**Diagnosis**

Platelet disorders are heterogeneous, and the diagnosis involves a repertoire of testing that can frequently be performed under the guidance of a pediatric hematologist and a specialized coagulation laboratory. The diversity of defects encompasses abnormalities of platelet adhesion, activation, aggregation, secretion, and signal transduction. Laboratory testing of platelet function abnormalities involves morphology, electron microscopy, flow cytometry, and platelet function studies.

Bleeding time is another test used to assess platelet function, although it has largely been abandoned by most laboratories for assessment of bleeding disorders. The test involves using a sphygmomanometer inflated to 40 mm Hg around the upper arm and making a 5-mm deep incision on the flexor surface of the arm. The time for cessation of bleeding is used to calculate bleeding time. The primary disadvantage of the test is the operator and interpretation variability. Results depend on room temperature, skin thickness, and patient cooperation. Bleeding time has been proven to lack utility in screening presurgical patients for a bleeding disorder in the absence of bleeding history or the assessment of platelet dysfunction in those who have mild thrombocytopenia (platelets <100,000/µL). Finally, the test can create anxiety for children.

PFA measures platelet adhesion, activation, and aggregation (primary hemostasis). The analyzer uses cartridges coated with platelet agonists such as collagen/epinephrine and collagen/ADP to measure closure times. A citrated blood sample is passed through the cartridges at high shear rate to simulate *in vivo* blood flow in the small capillaries. Platelets adhere to the cartridge membranes and occlude a small aperture centered in each membrane. The time, in seconds, for blood to occlude the aperture is referred to as closure time. A normal collagen/epinephrine closure time excludes the presence of a significant platelet function defect. If collagen/epinephrine closure time is prolonged and the collagen/ADP time is normal, aspirin-induced platelet dysfunction is the most likely cause. Prolongation of both tests may indicate anemia, thrombocytopenia, or a platelet function defect other than aspirin (eg, congenital platelet function disorders, vWD, platelet dysfunction due to uremia). Table 4 summarizes some of the common congenital platelet disorders.

**Specific Disorders**

Bernard-Soulier syndrome (BSS) is an autosomal recessive platelet function disorder that impairs platelet adhesion to...
vWF. The disorder is characterized by complete deficiency or lack of GPIb-IX-V receptor. Typical findings include prolonged PFA closure times, thrombocytopenia, and large platelets. Platelet aggregation response to ristocetin is important for diagnosis. Ristocetin is an antibiotic that causes vWF to bind to the platelet receptor GPIb-IX-V, inducing platelet aggregation in vitro. Due to deficiency or absence of the GPIb-IX-V receptor in BSS, platelet aggregation analysis shows absent or markedly reduced platelet aggregation to ristocetin. Aggregation to other agonists such ADP, epinephrine, and collagen is normal or reduced proportionally to the thrombocytopenia.

Glanzmann thrombasthenia is a rare autosomal recessive congenital disorder characterized by severe mucocutaneous bleeding. Platelet aggregation studies demonstrate absent or markedly impaired platelet aggregation to all agonists except ristocetin due to defects in the platelet receptor GPIIb-IIIa that binds to fibrinogen.

Disorders of platelet secretion and signal transduction comprise a diverse and complex group of disorders that involve impaired response to agonist stimulation and secretion of granule contents, which leads to impaired platelet aggregation response to ADP and epinephrine with or without impairment of responses to other agonists. Some of these disorders are delta storage pool disease and congenital defects in signal transduction due to platelet receptor abnormalities. Other disorders of platelets result from abnormal storage pool defects (storage pool deficiency or grey platelet syndrome), defects in platelet structural proteins (MYH9-related disorders such as May-Hegglin platelet disorder and X-linked thrombocytopenia), and disorders of platelet procoagulant activity (Scott syndrome). A pediatric hematologist should be consulted for appropriate evaluation and management of these conditions.

### Treatment

The bleeding management of patients affected with platelet disorders primarily focuses on preventing major and minor bleeding complications. Platelet transfusions are reserved for those with severe bleeding manifestations not controlled by conventional therapies, such as antifibrinolytics or DDAVP. Females with menorrhagia and congenital platelet disorder can be treated with oral contraceptive pills (OCPs) and antifibrinolytic therapy. Intrauterine devices are another option to reduce menstrual blood loss, especially if employed as a method to prevent pregnancy. Other therapies, such as recombinant FVII, are typically used for serious bleeding in patients who have severe congenital platelet disorders and in those patients who do not respond to platelet transfusions due to isoimmunization.

### RARE BLEEDING DISORDERS

Inherited deficiencies of other coagulation factors are less common than the previously described bleeding disorders and are described as rare bleeding disorders (RBDs). The RBDs are inherited quantitative or qualitative deficiencies of factors (fibrinogen [F1], FII, FV, FVII, FX, FXI, FXIII), combined FV and FVIII deficiency, congenital deficiency of vitamin K-dependent factors (VKCFD) with underlying defects in activation (γ-carboxylation) (FII, FVII, FIX, FX), and disorders of fibrinolysis (eg, PAI-1 deficiency, α2-antiplasmin

<table>
<thead>
<tr>
<th>NONSYNDROMIC CONGENITAL PLATELET DISORDERS</th>
<th>INHERITANCE</th>
<th>GENE (CHROMOSOME)</th>
<th>PREFERRED NONGENETIC LABORATORY TESTS</th>
<th>IMPORTANT FEATURES</th>
</tr>
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<tbody>
<tr>
<td>Bernard-Soulier syndrome</td>
<td>AR/AD</td>
<td>GP1BA (17p13) GP1BB (22q11) GP9 (3q21)</td>
<td>Blood smear LTA Flow</td>
<td>Giant platelets</td>
</tr>
<tr>
<td>Glanzmann thrombasthenia</td>
<td>AR</td>
<td>ITGB3 and ITGA2B</td>
<td>Blood smear LTA Flow</td>
<td>Normal platelets on morphology</td>
</tr>
<tr>
<td>Congenital amegakaryocytic thrombocytopenia</td>
<td>AR</td>
<td>MPL (1p34)</td>
<td>BM Bx</td>
<td>Megakaryocytic aplasia</td>
</tr>
<tr>
<td>Familial platelet disorder and predisposition to AML</td>
<td>AD</td>
<td>RUNX1 (21q22)</td>
<td>EM</td>
<td>MDS/AML risk</td>
</tr>
<tr>
<td>Gray platelet syndrome</td>
<td>AR</td>
<td>NBEAL2 (3p21.1)</td>
<td>EM</td>
<td>Myelofibrosis and splenomegaly</td>
</tr>
</tbody>
</table>

AD¼autosomal dominant, AML¼acute myeloid leukemia, AR¼autosomal recessive, BM Bx¼bone marrow biopsy, EM¼electron microscopy, Flow¼flow cytometry, LTA¼light transmission platelet aggregation, MDS¼myelodysplastic syndrome.
deficiency). Diagnosis is challenging because of the rarity of the disorders, variable clinical presentations, and sometimes the lack of family history.

RBDs may present in infancy or later in childhood. The most common manifestation is mucocutaneous bleeding. Bleeding manifestations of some of the disorders are peculiar; others have clinical manifestations similar to other disorders. The bleeding of F1 deficiency (afibrinogenemia) may be similar to that seen with moderate-to-severe hemophilia. Umbilical cord bleeding and mucosal bleeding are more characteristic of F1 deficiency. Severe FII deficiency presents early in childhood with mucosal and musculoskeletal bleeding and intracranial hemorrhage. Serious bleeding, such as umbilical cord bleeding, hemorrhagic ovarian cysts, hemoperitoneum during ovulation, and hemothrosis, are more common in FII deficiency than in other RBDs. FX and FXIII deficiencies are characterized by early onset of bleeding such as intracranial and umbilical cord bleeding. Umbilical cord bleeding is characteristic of FXIII deficiency, and usually bleeding symptoms are delayed because the role of FXIII is stabilization of the fibrin clot. Children affected with VKCFD present in early childhood with serious bleeding events, including intracranial hemorrhages.

Other factor deficiencies are not associated with clinical bleeding symptoms, such as FXII, prekallikrein, and high-molecular weight kininogen deficiencies. These disorders can cause prolongation of the aPTT. In addition, primary collagen and vascular disorders can mimic a bleeding disorder.

Disorders of fibrinolysis are characterized by delayed bleeding after a hemostatic challenge, such as dental extractions, trauma, or surgery. Menorrhagia is a common bleeding manifestation in disorders of fibrinolysis such as PAI-1 deficiency and α2-antiplasmin deficiency. Therapy is directed toward prevention of bleeding with the use of antifibrinolytic agents such as e-aminocaproic acid or tranexamic acid.

ACQUIRED BLEEDING DISORDERS

Acquired bleeding disorders typically are related to an underlying disease process. Liver disease can cause coagulopathy due to impaired hepatic synthetic capability. Chronic renal disease can cause abnormal platelet function associated with uremia. Intestinal malabsorption or chronic antibiotic therapy can cause vitamin K deficiency and consequently lead to VKCFD.

DIC is a consumptive coagulopathy characterized by intravascular activation of coagulation that leads to unregulated thrombosis and secondary fibrinolysis or inhibited fibrinolysis. Clinical manifestations involve thrombosis or bleeding, but the most frequently observed are bleeding, petechiae, and purpura related to consumption of platelets and coagulation proteins within the microvasculature. Among the common precipitating factors are sepsis through bacterial endotoxin release and activation/deposition of fibrin through the microvasculature, malignancy, and severe burns. Therapy primarily involves treating the underlying process and supportive care. The use of blood products (plasma, platelet concentrate) is not routinely indicated for abnormal laboratory findings but should be used to treat active bleeding. Asymptomatic patients at risk for bleeding complications, such as following surgery or invasive procedures, should be treated with replacement therapy. Anticoagulation might be indicated in patients with DIC who develop limb- or life-threatening arterial thrombotic events, purpura fulminans, or venous thromboembolism.

Hemorrhagic disease of the newborn is caused by vitamin K deficiency related to medications ingested by the mother that impair vitamin K metabolism or to the lack of vitamin K administration at birth. (8) The latter is becoming of increasing concern due to parental refusal of vitamin K administration based on personal or religious beliefs. Vitamin K deficiency due to maternal drug ingestion, such as anticonvulsants or warfarin, typically manifests in the first 24 hours after birth. Classic vitamin K deficiency presents during the first postnatal week with gastrointestinal bleeding, intracranial hemorrhage, bruising, and bleeding following circumcision. Exclusively breastfed infants are at higher risk due to marginal vitamin K content in human milk. Late vitamin K deficiency occurs between ages 2 and 12 weeks. Risk factors include exclusive breastfeeding, failure to receive vitamin K at birth, and disorders causing malabsorption such as cystic fibrosis.

Laboratory evaluation in vitamin K deficiency reveals prolonged PT and aPTT (if severe), with normal platelets and fibrinogen. The diagnosis can also be established by measurement of undercarboxylated prothrombin (PIVKA-II), which is released in the early stages of vitamin K deficiency. Vitamin K should be administered immediately to infants who are bleeding. The safest and most efficacious mode of replacement is subcutaneous administration; the intravenous route has been associated with rare anaphylactic reactions. Subcutaneous or intravenous administration can correct PT within 4 hours. Oral vitamin K can be given if absorption is not impaired, but correction of clotting times can take up to 8 hours after this route of administration. Fresh frozen plasma should be administered in addition to vitamin K if there is clinical evidence of bleeding. The American Academy of Pediatrics recommends that all term
infants receive 1.0 mg of intramuscular vitamin K at birth (0.3 mg for infants weighing <1,000 g; 0.5 mg for infants weighing >1,000 g and less than 32 weeks’ gestational age) as a preventive measure.

**THROMBOTIC DISORDERS**

Thrombotic events are less common in children than adults. Most of the causes of thrombosis in children are iatrogenic (such as the use of central venous access devices) or a combination of factors that can include an underlying disease (eg, malignancy, infection, congenital heart defects, nephrotic syndrome) and immobility, dehydration, obesity, or use of estrogen-containing medications. Some of the underlying pathogenic causes are alterations in procoagulant proteins such as FVIII and vWF (eg, elevation as an acute-phase reactant phenomenon), acquired abnormalities in normal plasma anticoagulants such as deficiency of AT secondary to medications (eg, asparaginase in leukemia therapy), or protein loss such as through nephrotic syndrome.

Congenital thrombophilic disorders should be considered when there is a family history of thrombosis, particularly at a younger age (eg, <50 years), unusual location of thrombosis, thrombosis without inciting factors (eg, intravenous catheter, surgery, fractures), or history of recurrent thrombosis. Congenital thrombophilia can increase the risk of thrombosis if an external high risk factor or a combination of risk factors is present concurrently (eg, prolonged immobilization after surgery). (9)(10)

Activated protein C resistance (APC-R) is the most common congenital thrombophilic disorder. APC-R is most commonly caused by a genetic defect in the FV gene, known as Factor V Leiden (FVL) mutation, which occurs in 3% to 8% of Caucasians and is less common in other ethnic groups. This genetic alteration causes arginine to be replaced by glutamine at position 506. The consequence is that activated protein C is unable to bind and inhibit FV. FV is a required cofactor for activation of FVIII and downstream generation of thrombin. Impaired inactivation of FVIII leads to increased generation of thrombin, which heightens the risk for thrombosis. FVL is inherited as an autosomal dominant trait. The APC-R ratio, a modified aPTT, is used as the screening test. A ratio of less than 2.0 suggests presence of the disorder, which can be confirmed through FVL gene mutation analysis. Heterozygous subjects have a threefold risk for venous thromboembolism; homozygous individuals carry a 30-fold increased risk. Children with this disorder do not develop a thrombosis unless another risk factor or underlying thrombotic disorder coexists. Heterozygous females appear to have a 30- to 60-fold increased risk for thrombosis with the use of OCPs. Acquired APC-R can be caused by autoantibodies directed against FV following exposure to bovine thrombin or some hematologic malignancies, pregnancy, OCPs, active thrombosis, or elevation of FVIII.

Prothrombin G20210A mutation is another congenital thrombophilic disorder present in approximately 1% to 2% of Caucasians. This disorder can increase thrombosis risk by 3 to 5 times compared to the general population. Homozygous deficiencies of protein S and C are incompatible with life. Neonates present with purpura fulminans at birth, and death is almost certain without prompt intervention. Hyperhomocysteinemia is associated with a risk for venous thromboembolism (VTE) or deep vein thrombosis (DVT), coronary artery disease, and stroke. Homocysteine is an intermediate amino acid produced by demethylation of methionine by methylenetetrahydrofolate reductase (MTHFR) in the folate cycle. Homocysteine requires vitamin B6, vitamin B12, and folate for its metabolism. Homozygous alterations in the MTHFR gene are found in 10% to 13% of the population and heterozygous alterations in 30% to 40%. Homocystinosy for the MTHFRc.667C>T is associated with a nearly 25% increase in plasma homocysteine. Elevation of homocysteine and MTHFR genetic alterations mildly increase the risk for VTE (odds ratio 1.27).

Antiphospholipid syndrome (APS) is one of the most common causes of acquired thrombophilia. Antiphospholipid antibodies (APAs) are directed to phospholipid-protein complexes and are associated with increased risk for both arterial and venous thrombosis. APAs can arise spontaneously (primary) or secondary to another condition (secondary) such as autoimmune disorders (eg, systemic lupus erythematosus). Diagnosis of APS requires both clinical findings (thrombosis) and laboratory criteria (positive lupus anticoagulant and/or anticardiolipin antibodies or β2GP1 antibodies [immunoglobulin G or M] in medium or high titers). Laboratory testing must be repeated at least 12 weeks from the first result in order to confirm the diagnosis. Lupus anticoagulant testing requires that 4 laboratory criteria are met for the diagnosis: 1) prolongation of at least 1 phospholipid-dependent assay (aPTT, dilute Russell Viper Venom Test [DRVVT], or hexagonal phospholipid neutralization screen), 2) evidence of inhibition by mixing patient plasma with normal plasma, 3) shortening of clotting times by addition of phospholipids (eg, DRVVT confirmatory ratio), and 4) absence of other inhibitors, such as anticoagulants or specific factor inhibitors. Arterial or venous thromboembolic events in the setting of APS require lifelong anticoagulation due to the high risk of recurrent thromboembolic complications.
THROMBOSIS EVALUATION, DIAGNOSIS, AND TREATMENT

Radiologic Evaluation

Different radiologic imaging modalities are available for diagnosing thrombosis, and the choice depends on the anatomic location of the thromboembolic event. Venography remains the standard modality for diagnosis, although its use in children is limited because of its invasive nature and the need for sedation. Doppler ultrasonography is the most frequently used radiologic modality for the diagnosis of DVT, but it lacks sensitivity for detecting DVT in the upper venous system. Specialized imaging techniques, such as computed tomography spiral technique (eg, evaluation for pulmonary embolism) and magnetic resonance imaging (eg, evaluation for stroke or sinovenous thrombosis) are also frequently used, depending on the location of the thrombotic event. Because acute thrombosis can lead to alterations in several pro- and anticoagulants, repeat testing at least 3 to 6 months following the thrombotic event and preferably off anticoagulation is recommended. Warfarin therapy can reduce not only vitamin K-dependent procoagulants such as FII, FVII, FIX, and FX but anticoagulants such as protein C and S as well. Diagnosis of a congenital or acquired thrombophilic disorder can help determine the appropriate duration of anticoagulation and counseling regarding prophylactic anticoagulation during high-risk situations (eg, pregnancy, surgery).

Oral Contraceptives and Thrombosis Risk

Estrogen-containing OCPs and hormonal therapy are associated with increased risk for venous and arterial thrombosis. The suggested mechanisms for increased thrombogenicity are APC-R; decreased concentrations of protein S; and increased concentrations of prothrombin, FVII, FIX, and FX in addition to impaired fibrinolysis due to increased concentrations of PAI-1 and thrombin activatable fibrinolytic inhibitor. The greatest risk period for thrombosis appears to be during the first 6 months to 1 year of OCP or hormonal therapy. Inherited or acquired thrombophilias can increase the risk of thrombosis with hormonal therapy and the often-asked question among clinicians is when to test for thrombophilia before the initiation of hormonal therapy. The natural risk of VTE in women is 1 to 2 cases per 10,000 women per year. OCPs increase this risk by 3- to 4-fold, pregnancy increases the incidence of thrombosis to 10 per 10,000 women-years, and the postpartum state is associated with a risk as high as 40 per 10,000 women-years. Importantly, in about 60% of VTEs occurring in women, no cause can be identified. Hereditary thrombophilia such as APC-R represents nearly 50% of the thrombotic events; 15% to 20% are due to AT; protein C, and protein S deficiencies. In OCP users, protein C deficiency increases thrombosis risk by 15-fold, while APC-R increases the risk of thrombosis by 35-fold. Several studies have addressed the utility of thrombophilia testing before OCP initiation, and the overall consensus supports not testing due to the lack of a cost-effective rationale and the potential negative effect on quality of life if the test result is positive. Even in high-risk groups, such as carriers of APC-R, only a few develop thrombosis during OCP or hormonal therapy, with an estimated 3 of 1000 carriers developing a thrombotic event. Selective screening in the setting of a positive personal and family history for thrombosis can be more cost-effective than universal or general screening. 

Thrombosis Treatment

Treatment of acute thrombosis requires anticoagulant therapy with either unfractionated heparin or low-molecular weight heparin (LMWH). If venous or arterial occlusion results in organ dysfunction or limb perfusion, thrombolytic therapy or mechanical thrombectomy should be considered emergently to preserve organ function. Heparin therapy can be monitored in different ways. Unfractionated heparin is monitored through prolongation of the aPTT or by anti-factor Xa (heparin) activity assays. LMWHs are monitored by the anti-factor Xa activity assay. The recommended duration of anticoagulation for most VTE events is 3 to 6 months if the thrombosis risk has resolved. If a child has developed VTE related to a central venous access device, the duration of anticoagulation might be shorter. If VTE is recurrent or idiopathic, as in the setting of congenital thrombophilia or acquired antiphospholipid syndrome, lifelong anticoagulation should be strongly considered due to the increased risk for thrombosis recurrence. Dosing and monitoring recommendations for unfractionated heparin, LMWH, and warfarin in the pediatric population are available as published guidelines. 

Heparin-induced thrombocytopenia (HIT) is a complication associated with the use of unfractionated heparin or LMWH that results in thrombocytopenia and further predisposition to thrombosis. The disorder presents with a decrease in platelet count that is greater than 50% from patient’s baseline platelet count before heparin initiation. The disorder is rare in children compared to adults (pediatric HIT incidence: 0%-2.3%). Diagnosis is established based upon clinical features and laboratory abnormalities.
The clinical criteria most commonly used in adults are the 4Ts, but this scoring system has not been validated in children. Laboratory testing involves screening assays such as enzyme-linked immunosorbent assay for the detection of anti-PF4/heparin antibodies (low-specificity immunoassay) and confirmatory assays such as serotonin release assay (high-specificity functional assay). When HIT is suspected, prompt discontinuation of heparin is recommended, followed by initiation of alternative anticoagulation (eg, argatroban, danaparoid, bivalirudin). (14)

If anticoagulation is required for an extended period of time (3 to 6 months) or for life, warfarin therapy should be considered and patients should be monitored with the international normalized ratio (INR) to ensure compliance with and adequacy of therapy. The INR is a laboratory measurement of PT prolongation of the patient compared to an international standard in the form of a ratio. The INR provides a standardized method of reporting the effect of oral warfarin on blood clotting. Therapeutic INR usually ranges between 2.0 and 3.0. An INR value above 4.5 increases the risk of major bleeding and a value less than 2.0 indicates subtherapeutic anticoagulation. Patients should be counseled about diet and medications that can interfere with INR testing, such as vitamin K-containing foods (eg, green leafy vegetables), antibiotics that alter gastrointestinal flora, and antiepilepsy medications. Novel anticoagulants offer the advantage of minimal or absent medication or diet interactions, easier administration (oral), and no need for therapeutic monitoring, but their use in children is limited due to the lack of systematic studies establishing safety and efficacy. Three direct thrombin inhibitors have been used in children (lepirudin, bivalirudin, and argatroban) intravenously, primarily as alternative anticoagulants in HIT. Oral preparations of newer anticoagulants are available (dabigatran, apixaban). Clinical trials in children are underway and their use in the pediatric group should be possible after completion of dosing, efficacy, and safety studies. Direct FXa inhibitors (rivaroxaban, apixaban, edoxaban) offer the advantage of anticoagulation independent of AT. Fondaparinux, a synthetic pentasaccharide FXa inhibitor that is chemically related to LMWH, is administered subcutaneously once a day. Dosing recommendations for children ages 1 to 18 years are available. Rivaroxaban is an oral FXa inhibitor, but its use in children is restricted due to lack of dosing recommendations. Some of the primary disadvantages to the use of novel anticoagulants are the lack of reversal agents and unavailability of laboratory assays to measure the anticoagulant effect, when necessary.

Extended follow-up evaluation is recommended in children after VTE or DVT due to the risk of postthrombotic syndrome related to venous insufficiency. Postthrombotic syndrome is characterized by swelling, pain, and skin ulcerations of the affected extremity. This disorder occurs more frequently in adults, but it is increasingly recognized in children following VTE or DVT early in life.

Summary

- On the basis of systematic studies as well as expert consensus opinion, one of the most important and useful tools for the diagnosis of a coagulation disorder is the clinical history and physical examination. (1)(2)(3)
- Individualized laboratory evaluation can assist in the initial confirmation or exclusion of a coagulation disorder.
- On the basis of several observational and case-control studies as well as expert consensus derived primarily from adult research, testing for thrombophilia is recommended in children if the knowledge of the defect facilitates preventive counseling and therapeutic decision-making (eg, anticoagulation duration, prophylaxis versus therapeutic interventions). (9)(10)(11)
- Referral to a pediatric hematologist might be indicated to confirm a diagnosis or when further diagnostic and management recommendations are required.
- Prompt diagnosis and management is often needed to prevent acute and long-term complications.

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此基于期刊的CME活动的截止日期为2018年12月31日，但学分记录将在参与者完成测验的年份。

1. A 4-month-old girl presents with gingival bleeding with tooth eruption and petechiae on the face and trunk suggestive of a disorder in primary hemostasis. Of the following, which is considered a key component of primary hemostasis?
   A. Antithrombin.
   B. Factor VIII.
   C. Fibrinogen.
   D. Platelets.
   E. Protein S.

2. A 2-day-old boy has excessive bleeding after circumcision. STAT laboratory tests reveal an activated partial thromboplastin time of 85 seconds and a factor VIII activity of less than 1%. The mother states that no one in the family has bleeding symptoms. Which of the following is a true statement regarding this patient?
   A. Because hemophilia A cannot be diagnosed in neonates, factor VIII activity should be assessed again in 6 months to confirm.
   B. The paternal family members should be tested for hemophilia or carrier status.
   C. The patient is at risk for spontaneous bleeding into the joints.
   D. The patient is unlikely to have congenital factor VIII deficiency given the lack of family history.
   E. Viral transmission from current factor replacement products is an ongoing problem for hemophilia patients.

3. A 6-year-old boy presents to the emergency department with prolonged gingival bleeding after dental extractions. His medical history includes prolonged bleeding after circumcision and frequent epistaxis. The patient’s mother and sister have anemia secondary to menorrhagia. Laboratory evaluation shows an abnormal platelet function analysis with a normal platelet count. Of the following, the most likely cause of this patient’s symptoms is:
   A. Activated protein C resistance.
   B. Bernard-Soulier syndrome.
   C. Factor XII deficiency.
   D. Hemophilia B.
   E. von Willebrand disease.

4. An otherwise healthy 16-year-old Caucasian girl who is sexually active asks you about birth control options. Her mother had a pulmonary embolism at 20 years of age while taking oral contraceptive pills. Of the following, the condition most likely to be a risk factor for thrombosis in this patient is:
   A. Antiphospholipid antibody syndrome.
   B. Factor V deficiency.
   C. Factor V Leiden mutation.
   D. Heparin-induced thrombocytopenia.
   E. Vitamin K deficiency.

5. A 10-month-old boy presents with a markedly swollen left knee and an 8-cm hematoma on the lateral thigh at the site of vaccine administrations. The mother denies any witnessed trauma. Of the following, the most likely laboratory finding in this patient would be:
   A. Decreased platelet count.
   B. Decreased von Willebrand activity.
   C. Prolonged activated partial thromboplastin time.
   D. Prolonged closure time on platelet function analysis.
   E. Prolonged prothrombin time.
Pediatric Coagulation Disorders
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