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## Coagulation Disorders

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# Coagulation Disorders

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

1. Determine when factor replacement should be given to patients who have hemophilia.
2. Describe the major long-term problems for hemophilia patients.
3. List the variables that affect von Willebrand factor measurements.
4. Delineate the most common risk factor for the development of deep vein thrombosis in children.
5. Characterize the normal range of coagulation proteins according to age.

## Introduction

Hemostasis is a process by which the body repairs damage to a blood vessel wall to prevent hemorrhage. At the site of injury, a hemostatic plug is formed by the interaction of the vessel wall, platelets, and coagulation factors. As the plug is formed, the coagulation system generates thrombin from prothrombin, thus initiating the formation of a fibrin clot (Fig. 1). This system is well controlled by multiple modulators and inhibitors at each step in the pathway. The major trigger for coagulation is the exposure of tissue factor (TF) in the injured vessel wall. TF binding to Factor VII (FVII), along with calcium and platelet-derived phospholipids, activates FX. FX, in conjunction with FV, prothrombin, calcium, and phospholipids, generates thrombin. Thrombin can initiate further thrombin production by the contact factor cascade (intrinsic pathway). It also converts fibrinogen to fibrin and activates FXIII to crosslink and stabilize fibrin. There are several inhibitors of this coagulation mechanism. Antithrombin (AT), heparin cofactor II, and alpha-2-macroglobulin directly neutralize the activity of thrombin. Protein C (PC), protein S (PS), and endothelial-bound thrombomodulin indirectly inhibit thrombin generation by inactivating FV and FVIII. A disorder of hemostasis can be manifested by either bleeding or thrombosis.

The hemostatic system is dynamic throughout childhood. Specifically, the concentrations of the vitamin K-dependent proteins (FII, FVII, FIX, FX) and contact factors (FXII, high-molecular weight kininogen, prekallikrein) are reduced in the first 6 months after birth. For the most part, children are more protected from thromboembolic disease than are adults because they have a decreased capacity to generate thrombin and an increased ability to inhibit thrombin by alpha-2-macroglobulin. Young children have twice the level of this inhibitor as older individuals. PC activity also is reduced throughout most of early childhood. Because of these differences, age-adjusted normal values need to be used.

## Bleeding Disorders

Several clues from the history and the physical examination may lead to the suspicion of a bleeding disorder, including the existence of a positive family history and the location,

## Abbreviations

<b>APCR:</b>	activated protein C resistance
<b>AT:</b>	antithrombin
<b>DDAVP:</b>	desmopressin acetate
<b>DIC:</b>	disseminated intravascular coagulation
<b>DVT:</b>	deep vein thrombosis
<b>F:</b>	factor
<b>INR:</b>	International Normalized Ratio
<b>LA:</b>	lupus anticoagulant
<b>LMWH:</b>	low-molecular weight heparin
<b>PC:</b>	protein C
<b>PFA:</b>	platelet function analyzer
<b>PS:</b>	protein S
<b>PT:</b>	prothrombin time
<b>PTT:</b>	partial thromboplastin time
<b>TF:</b>	tissue factor
<b>vWD:</b>	von Willebrand disease
<b>vWF:</b>	von Willebrand factor

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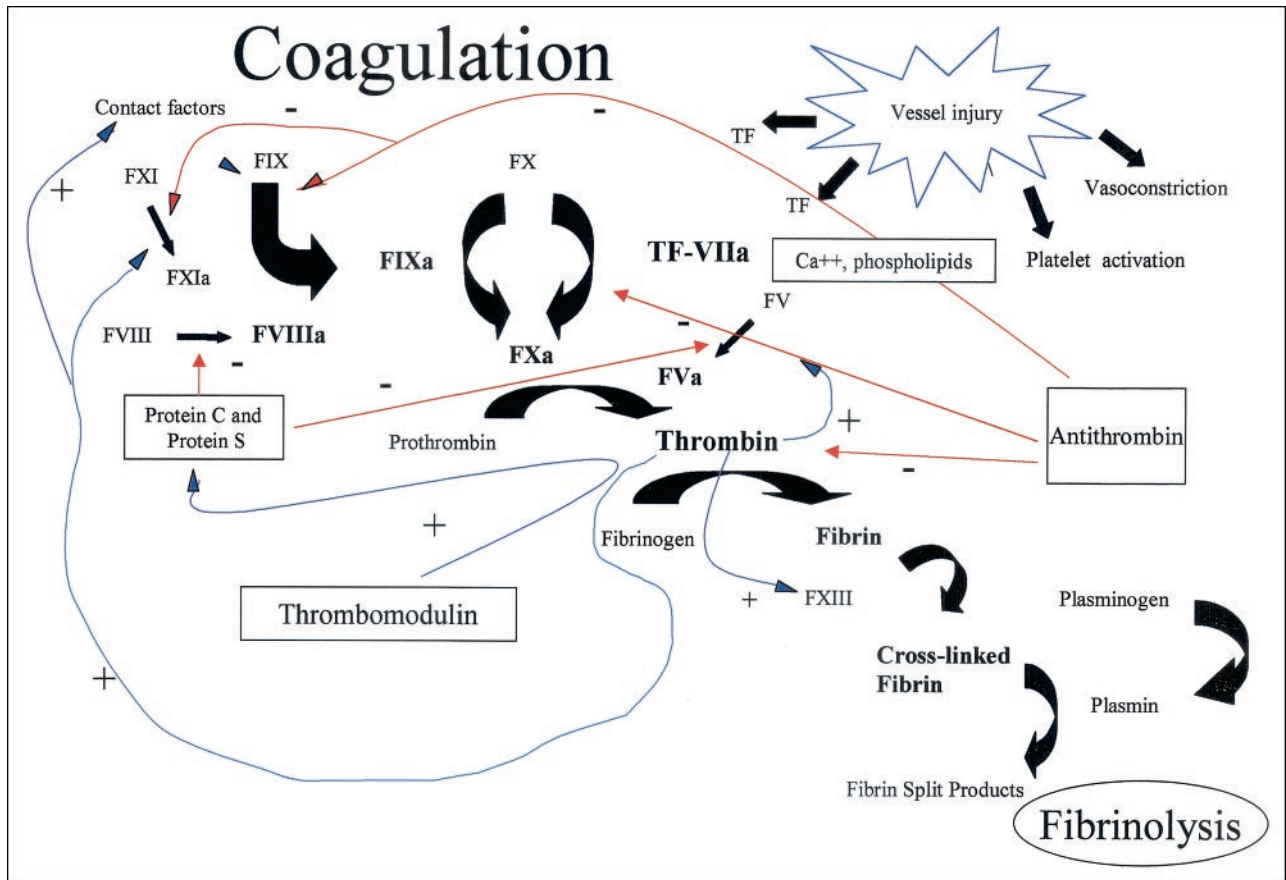


Figure 1. The coagulation system. F=factor, TF=tissue factor.

timing, and type of hemorrhage. General pediatricians often are confronted with the dilemma of a patient who has epistaxis, easy bruising, or menorrhagia. A bleeding disorder must be considered if the bleeding is severe or persistent, if there is bleeding from more than one site, or if a medical intervention such as iron replacement or transfusion is necessary. Disorders of primary hemostasis, suggesting an abnormality of platelets or small vessels, are characterized by immediate bleeding from trauma and present as petechiae or superficial ecchymoses. Conversely, impairment of secondary hemostasis (coagulation factor deficiencies) causes delayed bleeding after deep lacerations, surgery, or blunt trauma, with hemorrhage into subcutaneous tissues, joints, muscles, and abdominal viscera.

In the newborn period, bleeding with umbilical cord separation, after circumcision, or within the scalp or brain can be seen in patients who have hemorrhagic disorders. Toddlers present with superficial bruising and prominent deep-tissue bleeding that is more than expected for age. Teenage girls complain of menorrhagia

and may have associated anemia. Figure 2 provides guidelines for evaluating a suspected bleeding diathesis.

Hematologists frequently are consulted about a prolonged prothrombin time (PT) or partial thromboplastin time (PTT) in an asymptomatic child who has no history of bleeding. Although the majority of prolonged PTs or PTTs can be attributed to an error in obtaining or processing the sample, a lupus anticoagulant (LA) sometimes is identified. Generally, LA is associated with infection and is transient in young children. Despite causing a prolonged PTT, LA does not result in bleeding. In fact, paradoxically, it may cause thrombosis, although this problem occurs mostly in older patients who have autoimmune diseases. Occasionally, LA is associated with an acquired prothrombin deficiency manifested by a markedly prolonged PT as well as PTT. These patients may present with acute bleeding, but they rarely have long-term problems.

### Hemophilia

Hemophilia is a heterogenous genetic disorder that affects 1 in 5,000 males, resulting in lower circulating

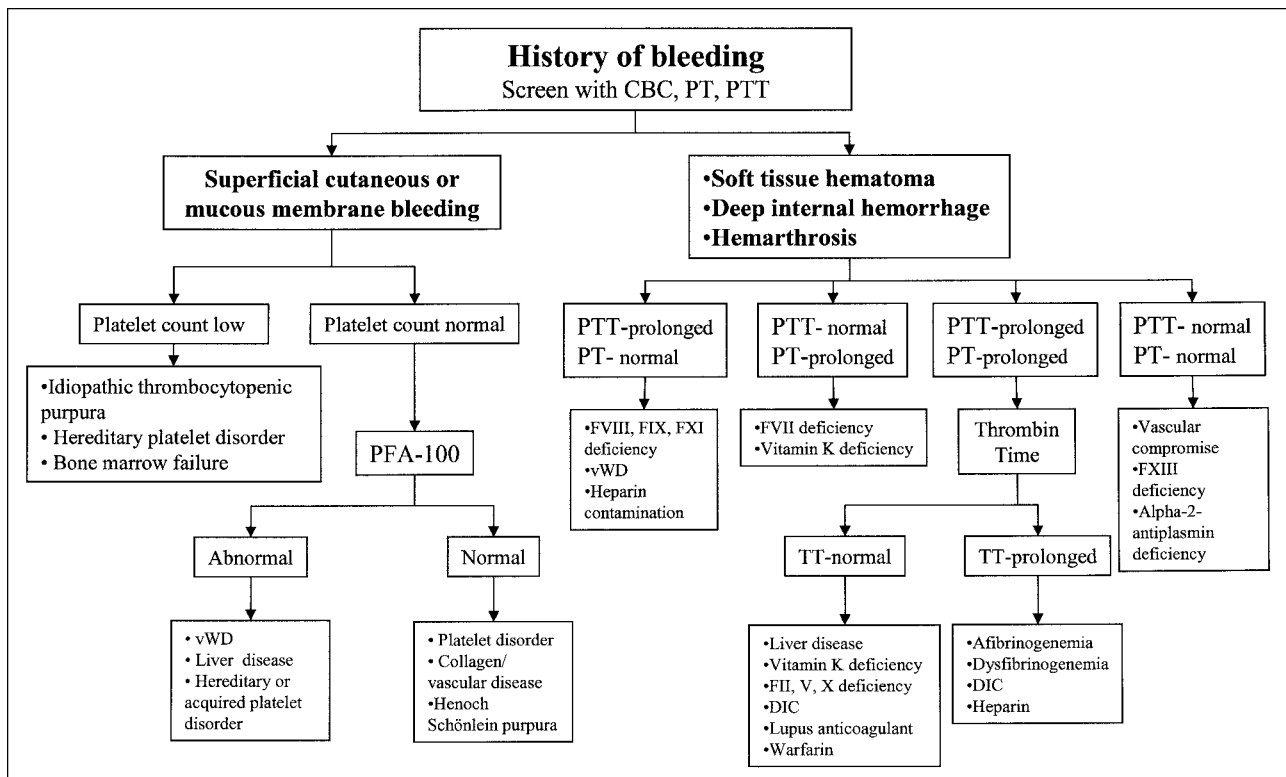


Figure 2. Approach to the bleeding patient. CBC=complete blood count, PT=prothrombin time, PTT=partial thromboplastin time, TT=thrombin time, F=factor, vWD=von Willebrand disease, PFA=platelet function analyzer, DIC=disseminated intravascular coagulation.

levels of functional FVIII or FIX. A deficiency of one of these factors causes hemorrhage because of delayed clot formation and an abnormally friable clot. Classic hemophilia (hemophilia A or FVIII deficiency) is the cause of hemophilia in 85% of patients; the remaining 15% have FIX deficiency (hemophilia B, Christmas disease). There is no racial predilection for the disease, which typically occurs in males via an X-linked pattern of inheritance. Any male infant born into a family in which hemophilia is known or suspected should be screened by measuring the FVIII or FIX level at the time of birth. FVIII levels in infants and adults are similar, making the diagnosis of hemophilia A accurate at an early age. FIX activity level, however, is lower in newborns than in adults and remains reduced through the first 6 months after birth. Hence, detecting mild or moderately severe hemophilia B may not be possible until a later age. DNA-based prenatal diagnosis is also available by chorionic villous sampling at 10 to 12 weeks' gestation. When hemophilia is identified, prophylactic factor infusion immediately after birth should be considered as a means of preventing intracranial hemorrhage. Because 30% of hemophilia patients

have new mutations and a negative family history, any male infant who has significant neonatal bleeding should be screened.

Hemophilia is characterized by hemorrhage, primarily into soft-tissue and joint spaces. Thirty percent of neonates present with profuse bleeding after circumcision, and 1% to 5% may have intracranial bleeding. However, most patients do not have soft-tissue hematomas until they start rolling over and crawling. The type of bleeding varies with the severity of the factor deficiency. Mild disease (6% to 30% factor activity level) is characterized by infrequent episodes of bleeding that occur primarily after surgery or trauma. Female carriers also can have factor levels as low as 30% and are prone to bleeding during surgery or pregnancy. Patients who have moderately severe hemophilia (1% to 5% factor activity level) have occasional hemarthroses and spontaneous hematomas and are at particular risk after even minor hemostatic challenges. Severe disease (<1% factor activity level) is characterized by spontaneous bleeding into joints and deep-tissue spaces.

Much of the treatment of hemophilia patients is

## Table 1. Factor Replacement Products and Guidelines in Hemophilia Therapy

### Products

- Recombinant FVIII
- Purified Plasma-derived FVIII
- Recombinant FIX
- Purified Plasma-derived FIX
- Porcine FVIII
- FIX Prothrombin Complex Concentrate (PCC)
- Activated PCC
- Recombinant FVIIa
- Desmopressin acetate: for mild disease

### Guidelines

- Minor bleeding (mouth, muscle, joint, sutures)  
—Achieve and maintain factor levels of 50% to 60%
- Major hemorrhage (head, gastrointestinal, large joint, or muscle; invasive procedures)  
—Achieve and maintain factor levels of 100%
- 1 U/kg of FVIII products = 2% rise in FVIII activity
- 1 U/kg of FIX products = 0.7% to 1% rise in FIX activity

home-based. Parents are taught early how to infuse factor intravenously. Some young patients have central venous catheters, such as tunneled infusion ports, to facilitate this type of therapy. Despite well-educated families and home infusion regimens, any affected patient may present acutely with symptoms warning of significant internal bleeding. The most severe hemorrhages involve the brain, spinal cord, throat, abdomen, and limb compartments. Severe headaches with or without neurologic symptoms may indicate an intracranial hemorrhage and demand immediate intervention. A child can complain of lower abdominal or groin pain and sensory loss over the anterior aspect of the thigh and knee during an iliopsoas muscle bleed. Painful swelling of any extremity may be a precursor to a compartment syndrome. Because of the potential severity of these complications, it is vital not to delay treatment of a patient known to have hemophilia. Factor replacement should be administered on presentation prior to further evaluation (Table 1).

Boys who have hemophilia are at risk for the chronic sequelae of repeated bleeding into joint spaces, including pain, arthritis, and limited range of motion. Young patients who develop “target joints” in which there is repeated bleeding should be placed on a regimen of prophylactic factor replacement in an effort to avoid progression of these chronic changes. Although viral

infections from contaminated factor products once were a problem, human immunodeficiency virus and hepatitis are nonexistent in today’s young population of hemophilia patients because of purified plasma-derived or recombinant factor concentrates. Another complication in patients receiving frequent factor infusions is the development of immunoglobulin G antibodies directed against FVIII or IX. These are discovered when a bleeding patient does not respond to therapy as expected or requires significantly more factor replacement. The inhibitory activity is measured by the Bethesda assay. One Bethesda unit per milliliter neutralizes 50% of the added FVIII or IX. High-titer inhibitors develop in 10% to 15% of patients and require alternative therapy for acute bleeding that bypasses the need for FVIII. A hematologist should be consulted for immune tolerance therapy or “desensitization” as well as for treatment of acute hemorrhage.

### von Willebrand Disease

von Willebrand disease (vWD) is the most common inherited bleeding disorder, affecting up to 1% of the population. von Willebrand factor (vWF) is a circulating plasma glycoprotein made up of high-, intermediate-, and low-molecular weight multimers. It has the ability to bind glycoprotein Ib and glycoprotein IIb-IIIa on platelet surfaces, thus stimulating platelet adhesion and aggregation at the injured vessel wall. vWF also is a carrier of FVIII and is vital for its stabilization in the circulation.

vWD is inherited in an autosomal dominant pattern with variable penetrance. Approximately 80% of cases are classified as type 1 disease, which is a quantitative deficiency in vWF and presents with mild bleeding symptoms; 15% to 20% of patients are classified as having type 2 disease (Table 2). Type 2A disease results from a qualitative deficiency of vWF in which there is an abundance of the small but an absence of the hemostatically effective large multimers, thus causing defective platelet adhesion at the site of vessel injury. In Type 2B vWD, platelet function is enhanced due to an increased affinity of vWF binding to glycoprotein Ib. There also may be associated thrombocytopenia. Type 2N disease is associated with decreased FVIII binding and mimics hemophilia. Finally, type 3 disease is a rare autosomal recessive disorder characterized by the absence of vWF and severe bleeding.

A positive family history, clinical history, and supportive laboratory findings make the diagnosis of vWD. Normal screening test results do not rule out the disorder, and repeated study sometimes is required because vWF levels can vary. The plasma concentration of vWF depends on age, race, and stresses such as exercise, trauma,

**Table 2. von Willebrand Disease**

Features	Type 1	Type 2A	Type 2B	Type 2N	Type 3
<b>Inheritance</b>	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive
<b>Bleeding time, PFA-100 Factor VIII</b>	Prolonged Normal or slightly reduced	Prolonged Normal or slightly reduced	Prolonged Normal or slightly reduced	Normal Reduced	Prolonged Markedly reduced
<b>vWF antigen</b>	Reduced	Normal or reduced	Reduced; increased affinity for platelets	Normal	Markedly reduced
<b>Ristocetin cofactor</b>	Reduced	Reduced	Reduced	Normal	Markedly reduced
<b>Ristocetin-induced platelet aggregation with low concentrations of ristocetin</b>	Absent	Absent	Increased	Absent	Absent
<b>vWF multimeric analysis</b>	Normal	Absence of large and intermediate multimers	Absence of large multimers	Normal	Variable
<b>Response to DDAVP</b>	Good response	Variable	DDAVP has been associated with thrombocytopenia	Variable	No response to DDAVP (treat with Humate-P [viral-inactivated intermediate-purity Factor VIII preparation with high vWF content])

PFA = platelet function analyzer, DDAVP = desmopressin acetate

and pregnancy. Initial screening tests include a complete blood count to rule out anemia and thrombocytopenia, PT/PTT, and a measure of bleeding time. Although historically the skin bleeding time test has been employed to evaluate bleeding signs and symptoms, it has limited usefulness because of a lack of specificity and precision. The platelet function analyzer (PFA-100) is a new in vitro measure of the bleeding time that allows more rapid evaluation and is more sensitive than the traditional bleeding time in the diagnosis of vWD. The PFA-100 is a high shear stress system that measures the time required for formation of a platelet plug that occludes the aperture in a membrane coated with collagen and either adenosine diphosphate or epinephrine. The amount of blood needed to perform the test is minimal, and the test is not operator-dependent. If the screening test results are abnormal, further study is indicated, including von Willebrand antigen, ristocetin cofactor (a functional test of vWF), FVIII level, and blood group. vWF measurements depend on blood group, with type O being associated with lower baseline levels of vWF antigen and activity. In general, patients who have vWD have a prolonged bleeding time or PFA-100 test result, normal PT, normal or slightly prolonged PTT, and low vWF activity. vWF multimer analysis and other special studies can determine specific subtypes of vWD. Type 2B can be screened by measuring ristocetin-induced platelet aggregation using low concentrations of ristocetin. Knowing the type of vWD may be important for determining therapy.

Treatment of vWD depends on the severity of bleeding. Desmopressin acetate (DDAVP) is a synthetic analogue of vasopressin that, when administered at an intravenous dose of 0.3 mcg/kg, increases the level of vWF and FVIII within 1 hour by mobilizing the platelet and endothelial cell stores of vWF and stabilizing FVIII. Before DDAVP becomes part of the treatment plan, a patient who has vWD type 1 or Type 2A should receive a DDAVP challenge. Responsiveness to DDAVP can be determined by measuring vWF levels (and the PFA-100 results, if available) before and after intranasal or intravenous administration. If the factor levels rise into the normal range, DDAVP can be used to treat or prevent bleeding. DDAVP can be administered every 12 to 24 hours as needed for bleeding symptoms. Intranasal DDAVP is available as 1.5 mg/mL of desmopressin and is administered at a dose of 150 to 300 mcg. The dilute form used for enuresis

and diabetes insipidus is not effective. In patients who have Type 2B vWD, the use of DDAVP has been associated with thrombocytopenia. Other adverse effects of DDAVP include facial flushing, tachycardia, headache, and hyponatremia. Therefore, it is used cautiously in infants. Because of the phenomenon of tachyphylaxis, the efficacy of DDAVP in the prevention and treatment of bleeding may diminish over several days. For acute bleeding that does not respond to DDAVP, a factor VIII-vWF concentrate should be given. Because many adolescent girls who have vWD initially present with menorrhagia, it is important to diagnose and treat any associated anemia in addition to preventing heavy menses with oral contraceptives or monthly courses of DDAVP.

### Uncommon Bleeding Disorders

Other known autosomal recessive bleeding disorders are rare. FXI deficiency may cause mild bleeding. FXIII deficiency results in an inability to crosslink fibrin and can manifest as severe hemorrhage from the umbilical cord or in the brain. Deficiencies of FII, FV, FVII, and FX also may cause severe bleeding when the factor levels are extremely low. Afibrinogenemia or dysfibrinogenemia is associated with a variable clinical course. Treatment for all of these conditions involves factor replacement by intravenous infusion.

Cryoprecipitate, fresh frozen plasma, or prothrombin complex concentrates generally are used to treat hemorrhage, depending on the diagnosis. Although other factor deficiencies (FXII, prekallikrein, high-molecular weight kininogen) can present with a prolonged PTT, they do not cause bleeding symptoms, so no therapy is needed. Primary collagen/vascular disorders can mimic a hemostatic abnormality. Ehlers-Danlos syndrome typically presents with prominent ecchymoses along with hyperextensible joints and skin, and the most severe form is associated with rupture of medium or large arteries. Hemangiomas and hereditary hemorrhagic telangiectasia are vascular proliferative disorders that can manifest with significant bleeding symptoms involving the airways and the gastrointestinal tract.

### Acquired Bleeding Disorders

Bleeding frequently develops as a complication of other disease processes. Liver disease can cause vitamin K and coagulation factor deficiencies. It also is associated with

splenic sequestration of platelets. Uremia and chronic renal disease are associated with altered platelet function and angiodyplasia. Syndromes characterized by vasculitis, such as Henoch-Schönlein purpura, may mimic a bleeding disorder despite normal hemostatic parameters.

Hemorrhagic disease of the newborn caused by vitamin K deficiency can present in the first 24 hours after birth due to medications ingested by the mother, such as anticonvulsants and warfarin. However, it is seen more commonly in the first week to several months after birth. Generally, affected infants are delivered at home and are breastfed. Children who have cystic fibrosis or other disorders associated with steatorrhea also can develop vitamin K deficiency. Hemorrhage can be prevented by prophylactic injection of vitamin K after delivery.

Deposition of fibrin in the microvasculature and consumption of platelets and procoagulant proteins characterize disseminated intravascular coagulation (DIC). Clinical manifestations include oozing from puncture sites and mucous membranes. Petechiae and palpable

**Although thromboembolic events occur uncommonly in children, deep vein thrombosis is becoming an increasingly recognized phenomenon in pediatrics.**

purpura are usually present, especially when associated with endotoxin-mediated sepsis. Supportive care includes maintaining platelet counts greater than  $50 \times 10^3/\text{mcL}$  ( $50 \times 10^9/\text{L}$ ) and fibrinogen above  $100 \text{ mg/dL}$  ( $1.0 \text{ g/L}$ ). Fresh frozen plasma can be given, although it rarely normalizes hemostasis. DIC always is a secondary event; the underlying cause (sepsis, malignancy, trauma, or Kasabach-Merritt syndrome) must be treated successfully to correct the coagulopathy.

### Thrombotic Disorders

Although thromboembolic events occur uncommonly in children, deep vein thrombosis (DVT) is becoming an increasingly recognized phenomenon in pediatrics. Children can have genetic risk factors for thrombus development, but most thromboembolic events in children are associated with an underlying medical condition, such as malignancy, sepsis, nephrotic syndrome, or congenital heart disease. Most of these conditions or their therapies cause a deficiency of proteins such as AT or PC or an

elevation of inflammatory mediators such as FVIII and vWF. The most common risk factor for thrombus formation is the presence of a central venous catheter. Central lines are used commonly in critical care and to facilitate the chronic administration of chemotherapy and total parenteral nutrition. Because central venous catheters are placed more often in the subclavian or jugular veins in children, most DVTs occur in the upper venous system. DVT may present with extremity swelling and pain or pulmonary emboli. Arterial thrombosis frequently is seen in neonates requiring umbilical catheters and in patients who have congenital heart disease and are undergoing cardiac catheterization.

Thrombophilia, or the genetic predisposition to form venous or arterial clots, must be considered if there is a positive family history, if there is a history of recurrent clots, if thrombi are in unusual locations, or if there is thrombosis at an early age. The incidence of the genetic mutations leading to hypercoagulability is highest in the Caucasian population. Having thrombophilia in conjunction with an acquired insult greatly increases the risk of a child having severe or recurrent thrombotic disease.

## Thrombophilia

### Activated Protein C Resistance

The most common genetic disorder causing thrombophilia is activated protein C resistance (APCR), usually caused by the factor V Leiden mutation that occurs in 3% to 8% of Caucasians but fewer than 1% of African-Americans. This single point mutation in the FV molecule, in which the arginine is replaced by glutamine at position 506, is inherited in an autosomal dominant pattern. APCR predisposes to DVT because the natural anticoagulant, activated PC, is unable to bind and inhibit the activated FV molecule. The APCR ratio, a modification of the PTT, can be ordered as a screening test. An APCR ratio of less than 2.0 generally is considered abnormal. Abnormal test results should be confirmed by a polymerase chain reaction assay for the FV Leiden mutation. Heterozygous individuals have a threefold increased risk of venous thromboembolism, but persons who are homozygous for the mutation have up to a 30-fold increased risk. Although 30% of patients who have APCR develop thrombosis before middle age, most children do not have problems unless another risk factor is present. Acquired ACPR also can be seen in association with pregnancy and oral contraceptive use.

### Prothrombin 20210A Mutation

Approximately 1% to 2% of Caucasians are heterozygous for the prothrombin 20210A mutation, which is associ-

ated with a three to five times increased risk for development of a DVT by early adulthood.

### Hyperhomocystinemia

Mutations in the genes for cystathionine beta-synthase and methylenetetrahydrofolate reductase cause elevated plasma homocysteine levels. Whereas most of the other genetic thrombophilias cause DVT, hyperhomocystinemia rarely causes either arterial or venous thrombotic disease in childhood.

### Deficiency of Antithrombin, Protein C, or Protein S

Homozygous AT deficiency is incompatible with life. Homozygous deficiency of PC or PS causes purpura fulminans within hours of birth. Affected patients also can show signs of in utero ophthalmic, cerebral, or large vessel occlusions. Most infants do not survive the newborn period without aggressive intervention. However, heterozygous deficiencies cause much milder prothrombotic states. Persons who have these deficiencies have a 50% risk of developing thromboembolism by middle age. Although children generally are unaffected, these disorders can be unmasked at an early age when additional prothrombotic triggers are added.

### Lipoprotein(a)

Elevated lipoprotein(a) is associated with cardiovascular disease in adults, but it also is known to have antifibrinolytic properties that make it a risk factor for the development of venous thromboembolic disease. Serum levels of greater than 30 mg/dL (0.3 g/L) increase the likelihood of thromboembolism in childhood by a factor of seven.

## Diagnosis, Treatment, and Long-term Considerations of Thrombotic Disease

Evaluating hypercoagulability, inherited or acquired, involves first confirming the diagnosis of DVT. The gold standard test is venography, but Doppler ultrasonography, spiral computed tomography, and magnetic resonance imaging also have been used. Unfortunately, Doppler ultrasonography is not a sensitive test for DVT of the upper venous system. Identifying congenital deficiencies at the time of diagnosis of DVT may be difficult because levels of coagulation proteins such as PC and AT may be low during acute sepsis, malignancy, or a flare of systemic lupus erythematosus. The tests ideally should be performed 3 to 6 months after the acute event to confirm a congenital problem and to help determine the length of anticoagulant therapy. Warfarin therapy will reduce PC and PS values, so the laboratory evaluation should be



### Table 3. Laboratory Tests for Hypercoagulability

#### Strongly suggested

- Activated Protein C Resistance Ratio (APCR)
  - Factor V Leiden mutation if APCR is abnormal
- Prothrombin 20210A mutation
- Protein C activity
- Protein S activity
- Antithrombin activity
- Antiphospholipid antibodies
- Lupus anticoagulant panel

#### Other tests to consider

- Plasma homocysteine
- Lipoprotein(a)
- Factor VIII

performed off of oral anticoagulation. Family studies often can be helpful in these situations. Table 3 describes the evaluation for thrombophilia.

Once a congenital prothrombotic state is identified, patients need to be counseled about the risk of future thromboembolic events. Girls should be cautioned about DVT associated with oral contraceptive use and pregnancy. Prophylaxis against thrombi is considered in situations of prolonged immobilization, surgery, or serious infection. Treatment of an acute thrombus is initiated with unfractionated or low-molecular weight heparin (LMWH). If the occlusion is life-threatening, immediate thrombolytic therapy with tissue plasminogen activator or recombinant urokinase should be considered with the assistance of the hematologist and intensive care team. Patients then are changed to oral warfarin or continue LMWH for at least 3 to 6 months. After that period, anticoagulation should be considered for prevention during high-risk situations. Children who have no underlying predisposition for thromboembolism but develop a DVT associated with a central venous catheter do not require long-term therapy. However, patients who have recurrent or severe DVT and a known thrombophilia mutation probably require lifetime anticoagulation.

Close follow-up is necessary by monitoring the Inter-

national Normalized Ratio (INR) for patients receiving warfarin or the anti-factor Xa level for patients receiving LMWH. Because these medications have the potential to induce osteoporosis, careful assessment of bone density and growth also is necessary. Any patient who has a history of DVT has the potential to develop pulmonary embolism, recurrent thrombosis, or postphlebotic syndrome characterized by chronic pain and swelling and discoloration of the affected extremity. However, the frequency of these complications in children is unknown. The problem of DVT in children who have central lines only now is beginning to be appreciated fully. Even though we have used long-term catheters for the past 25 years, we do not know the incidence of DVT in this setting, nor do we know if subacute or chronic DVT has serious sequelae.

### Conclusion

Diagnosing a coagulation disorder involves taking a careful history and confirming the findings with laboratory evidence. A correct diagnosis is necessary to determine initial and long-term therapy as well as for genetic counseling. The general pediatrician should be able to perform the appropriate screening tests and to interpret them correctly. Once a diagnosis is suspected or confirmed, consulting a pediatric hematologist to determine long-term management is recommended.

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## PIR Quiz

Quiz also available online at [www.pedsinreview.org](http://www.pedsinreview.org).

6. The parents of a 3-year-old African-American girl report that the mother's sister has an 8-month-old boy who has just been diagnosed as having hemophilia A. There is no other family history of hemophilia. They have read a good deal of information on the Internet and want to know if the information is correct. Which of the following information is *correct*?
  - A. Any future male children of this couple have a 25% chance of having hemophilia.
  - B. Fifty percent of patients who have hemophilia have hemophilia A.
  - C. The disorder is rare in African-Americans.
  - D. Their daughter has a 25% chance of having hemophilia.
  - E. Thirty percent of children who have hemophilia constitute new mutations who have no family history.
7. The *most* common presentation of hemophilia is:
  - A. Bleeding following circumcision.
  - B. Epistaxis.
  - C. Hematuria.
  - D. Intracranial hemorrhage following vaginal delivery.
  - E. Soft-tissue swelling after the first few months of life.
8. During your initial visit with the family of 4-year-old boy who is new to your practice, you learn that the boy's father has von Willebrand disease. In answering their questions about the disorder, which of the following is correct?
  - A. Blood type A is associated with lower factor VIII levels.
  - B. It usually is inherited as an autosomal dominant disorder with complete penetrance.
  - C. It usually is inherited as an autosomal recessive disorder.
  - D. The disease affects as many as 1% of the general population.
  - E. The disease is related most commonly to a qualitative disorder of von Willebrand factor.
9. An 8-year-old child who has no prior medical problems develops pain, swelling, and a tender cord in the popliteal region. Doppler ultrasonography reveals a deep vein thrombosis. In considering further evaluation, which of the following is *correct*?
  - A. Activated protein C resistance is found in 3% to 8% of Caucasians.
  - B. Family studies rarely are helpful.
  - C. Levels of congenitally deficient factors rarely are affected by concomitant medical conditions.
  - D. Oral anticoagulants reduce the levels of protein C and antithrombin III.
  - E. Prothrombin 20210A is rare, and the test for it is not performed routinely.
10. A 10-year-old boy develops pain and swelling of his left calf followed within several hours by moderate respiratory distress. Doppler ultrasonography confirms the presence of a deep vein thrombosis in his femoral vein, and a ventilation perfusion scan reveals a small right-sided pulmonary embolus. He had a deep vein thrombosis in his right leg 2 years ago, at which time he was found to have the prothrombin 20210A mutation. The *most* appropriate therapy for this child is:
  - A. Lifelong antiplatelet therapy.
  - B. Lifelong therapy with oral anticoagulants.
  - C. Observation and treatment with oral anticoagulants if pulmonary embolus occurs.
  - D. Three months of low-molecular weight heparin therapy.
  - E. Three months of oral anticoagulant therapy.

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