

Bleeding Disorders

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

1. Discuss the physiology of hemostasis.
2. Describe the clinical features suggestive of an underlying bleeding disorder.
3. Develop a diagnostic algorithm for evaluating patients who are suspected of having bleeding disorders.
4. Recognize the inheritance and clinical management of the commonly encountered bleeding disorders.

Overview of Hemostasis

Hemostasis refers to the process whereby bleeding is halted in a closed circulatory system. Understanding the physiology of hemostasis allows the clinician to identify children who have both inherited and acquired abnormalities of hemostasis, guide laboratory investigations, and facilitate effective therapeutic interventions.

In response to an injury (Fig. 1), local vasoconstriction reduces blood flow to limit or prevent bleeding. Primary hemostasis describes the subsequent interaction between platelets, von Willebrand factor (vWF), and the vessel wall to form a platelet plug at the site of vascular injury. vWF, a large multimeric plasma glycoprotein that is synthesized and stored in endothelial cells and megakaryocytes, is released at the site of vascular injury. Circulating vWF also binds and stabilizes factor VIII (FVIII). Exposed subendothelial elements, such as collagen, serve as a binding site for vWF, which, in turn, mediates platelet adherence to the area of injury. Platelet receptors, vWF, and fibrinogen mediate platelet-platelet interactions, leading to aggregation, activation, secretion of platelet granules, and additional platelet aggregation. The platelet plug that ensues contributes to bleeding cessation but is unstable. Thus, for stability, the platelet plug must be reinforced by the formation of an organized fibrin clot through the activation of the blood coagulation system or secondary hemostasis.

Blood coagulation involves a cascade of activation reactions. At each stage, a precursor protein (eg, FX) is converted to an active protease (eg, FXa) in the presence of calcium and a phospholipid surface that is provided by damaged endothelium and platelets.

Coagulation is initiated through the “extrinsic pathway.” Following injury, the damaged endothelium expresses tissue factor (TF). TF binds to FVII and forms the TF/FVIIa complex, which activates FIX and FX. FXa activates prothrombin to thrombin, the central mediator of coagulation. Thrombin has many functions within coagulation as well as other physiologic pathways. However, its prime function in hemostasis is to convert soluble fibrinogen into insoluble fibrin. These fibrin monomers polymerize in the vicinity of the primary platelet plug and are strengthened further through cross-linking by FXIII. However, the initial FXa and thrombin generated through the extrinsic pathway are inadequate to form an effective fibrin clot. Therefore, a feedback loop, the “intrinsic pathway,” also is activated by thrombin. Thrombin can activate FXI, which, in turn, activates FIX to FIXa. This reaction further enhances FXa and thrombin generation. This merger of the extrinsic and intrinsic pathways has been called the “common pathway.” In addition, thrombin activates two key cofactors of coagulation, FVIII and FV. FVIIIa is a cofactor for FIXa, enhancing its proteolytic activity on FX by several orders of magnitude. FVa is a cofactor for FXa, which enhances the proteolytic activity of FXa on prothrombin.

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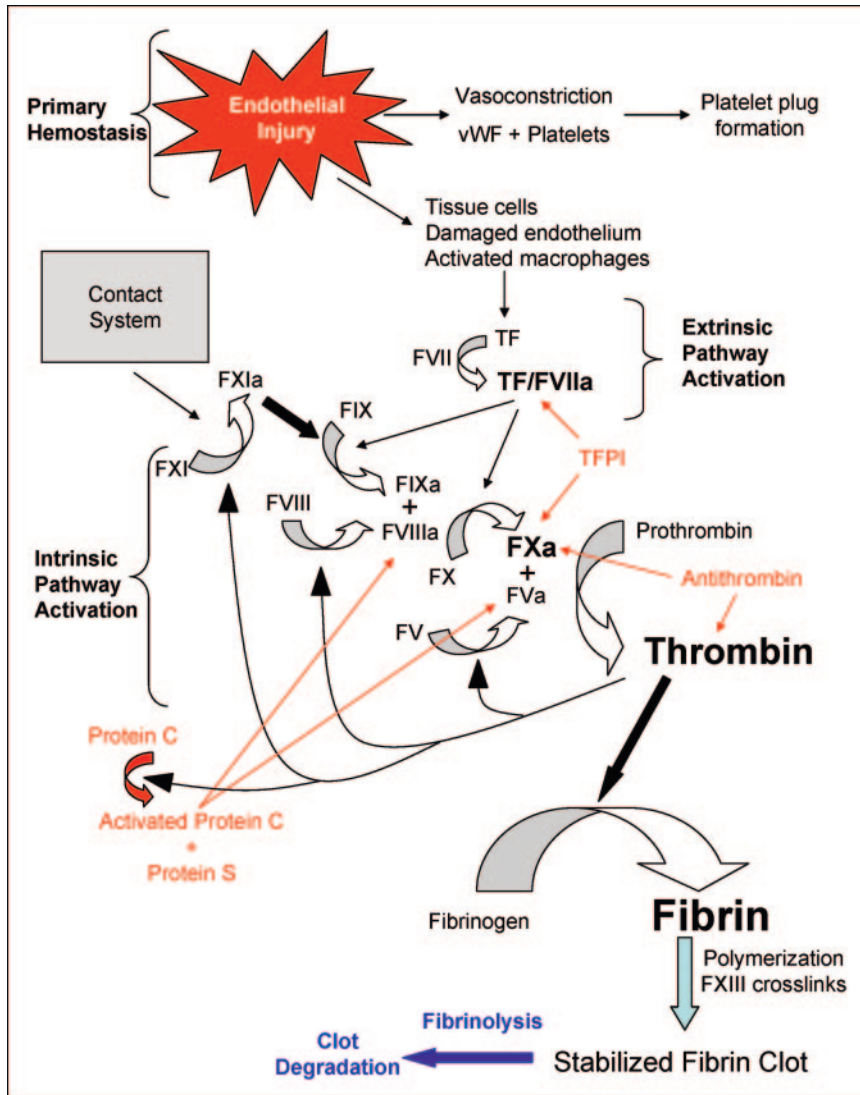


Figure 1. The coagulation system. F=factor, vWF=von Willebrand factor, TFPI=tissue factor pathway inhibitor. Coagulation inhibitors are indicated in red.

This effect ultimately produces a burst of thrombin formation sufficient for effective hemostasis. The physiologic significance of this amplification loop in hemostasis is exemplified by the severe bleeding manifestations associated with a deficiency of one of its components (eg, FVIII deficiency resulting in hemophilia A).

Physiologic inhibitors of coagulation regulate each step of the hemostatic process. Within the extrinsic pathway, tissue factor pathway inhibitor binds to and inhibits the action of TF/FVIIa and FXa. Protein C is activated by thrombin to activated protein C that, along with its cofactor protein S, proteolytically inactivates FVIIIa and FVa, thereby inhibiting the intrinsic pathway.

Antithrombin is the key inhibitor of the common pathway, forming complexes with FXa and thrombin. Following formation of the fibrin clot, a fibrinolytic pathway mediated by plasmin regulates the size of the clot and ultimately facilitates its dissolution.

The plasma kallikrein/kinin system includes FXII, prekallikrein, and FXI. These proteins also are known as the “contact system” because FXII autoactivates when associated with a negatively charged surface such as a glass tube. The autoactivation of FXII results in prekallikrein activation and additional amplification of FXII, producing subsequent activation of FXI, which can contribute to activation of the intrinsic pathway. However, deficiencies of FXII and prekallikrein are not associated with bleeding. Therefore, this system cannot be a physiologic one for hemostasis, but it is useful clinically in the activated partial thromboplastin time (PTT) to evaluate components of the intrinsic pathway.

The Influence of Age on the Coagulation System

Most coagulation factors are found in the fetus by the 10th week of gestation, with synthesis predominantly by the liver. Protein production increases with gestational age

and through the first year of postnatal life when the plasma activity for most coagulation factors becomes comparable with that of adults. In the immediate postnatal period, concentrations of vitamin K-dependent coagulation proteins (prothrombin, FVII, FIX, and FX) and the inhibitors protein C and protein S are approximately 50% of adult values. In contrast, values for fibrinogen, FVIII, FV, FXIII, and inhibitors are similar to or increased above adult values. Concentrations of vWF are increased at birth and for the first several postnatal months. In the clinical setting, the results of various coagulation assays need to be interpreted according to age-appropriate normal ranges.

Evaluation of a Child Who Has a Bleeding Disorder

Children who have bleeding disorders often present initially to their pediatricians with suspicious signs, abnormal screening laboratory results from a presurgical evaluation, or a known family history. Whereas severe bleeding disorders such as hemophilia often present in the first year after birth, less severe bleeding disorders, such as von Willebrand disease (vWD) or a platelet function abnormality, may be clinically silent for years until a major hemostatic challenge occurs. Careful assessment of the medical and the family history, attention to pertinent physical findings, and discretionary use of laboratory resources are required to reach a likely diagnosis and initiate definitive therapy.

Clinical Evaluation

A systematic approach employing the following questions can help to reach a more precise clinical diagnosis.

AM I DEALING WITH A BLEEDING DISORDER? Typical presentations include easy bruisability, mucosal bleeding (epistaxis; menorrhagia; oral, genitourinary, or rectal bleeding), unexpected surgical hemorrhage, and deep-tissue bleeding into muscles and joints. Because many of these signs can be common in childhood, the challenge for the pediatrician is to decide when additional evaluation is warranted. The significance of any particular bleeding sign is enhanced when seen in combination with other bleeding signs or when evaluated in relation to the presence or absence of associated trauma.

Bruising in children first must be differentiated from extrinsic causes such as child abuse, which is more common than hemophilia. Inflicted trauma is most likely to manifest over the calvarium, the chest, the back, and the long bones and may retain the outlines of the instrument. Bruises associated with a defect in primary hemostasis usually are located over areas of typical childhood trauma, such as the bony protuberances of the extremities or the spinous processes along the back, typically are superficial, and are in multiple stages of resolution. Petechiae may suggest platelet dysfunction or vWD. In general, bruises that are not limited to the distal extremities, are larger than a quarter coin, and are associated with hematomas and bruising out of proportion to the mechanism of injury are more indicative of an underlying hemostatic disorder. Intramuscular hematomas may be more difficult to see, but they cause swelling of the muscle group and pain with use of the muscle. Hemarthrosis (bleeding into a joint) causes joint effusion, warmth, and pain with passive movement of the joint and

is a common feature of hemophilia. For young children, refusal to walk or use the affected limb may be the only apparent sign.

Epistaxis is a common childhood complaint and most likely is due to local factors such as drying of the nasal mucosa, trauma, or allergic rhinitis. However, among patients referred to a pediatric hematology clinic for recurrent epistaxis, 25% to 33% are diagnosed as having a bleeding disorder. Epistaxis requiring an emergency department visit, occurring in both nostrils, and occurring in association with other bleeding signs and a family history of similar bleeding increases the likelihood of an underlying bleeding disorder.

Menorrhagia may be the presenting sign in an adolescent girl who has a bleeding disorder and often can occur with the first cycle at menarche. Menorrhagia frequently is associated with anemia and a suboptimal quality of life. A pictorial blood flow assessment chart can be used in the office to provide a semiquantitative assessment of menstrual blood loss. Frequent pad changes (<2 h frequency), menses lasting more than 7 days, or more than one menstrual period per month all are consistent with menorrhagia. In 2000, the American College of Obstetrics and Gynecology recommended that women who have menorrhagia be evaluated for vWD. Platelet function disorders and other coagulopathies also are frequent causes of menorrhagia.

Surgical bleeding in children is associated most often with circumcision, tonsillectomy, and dental extractions. In addition to uncontrolled bleeding in the surgical field, bleeding in an affected individual may extend beyond the surgical site (ie, drains, vascular access), with associated poor wound healing and infection. The need for transfusion during or after surgery that normally does not cause significant blood loss can suggest an underlying bleeding disorder. Bleeding after tonsillectomy or adenoidectomy often is delayed until 7 to 10 days postoperatively when there is an underlying bleeding disorder.

WHAT IS THE CLINICAL PHENOTYPE OF THE BLEEDING?

Mucosal bleeding characterized by easy bruisability, epistaxis, menorrhagia, petechiae, and oozing from surgical wounds is most consistent with a defect in primary hemostasis. The pediatrician should consider defects in platelets, vWF, or the vessel wall. On the other hand, deep-tissue bleeding (hematomas, joint and muscle hemorrhages) and “delayed” surgical bleeding are more suggestive of a coagulation factor abnormality. The most common disorder in this group is hemophilia, but other rare clotting factor deficiencies can occur.

IS IT CONGENITAL OR ACQUIRED? Inherited severe bleeding disorders present most often during the neonatal period or early childhood. Circumcision bleeding, umbilical stump bleeding, cephalohematomas, and subgaleal hemorrhages following delivery all may occur in otherwise healthy infants but are cardinal manifestations of underlying bleeding disorders. Hence, these signs always should be evaluated with a high degree of suspicion. The incidence of neonatal intracranial hemorrhage among boys who have hemophilia is estimated to be as high as 3%, but may be as high as 25% in patients who have FXIII deficiency. Diagnosis of a bleeding disorder in this setting is urgent because specific replacement therapy is required to prevent extension of the hemorrhage.

Only two thirds of patients who have hemophilia have a positive family history of the condition. Therefore, a high degree of suspicion is required, even with a negative family history. Because hemophilia is an X-linked disorder, the history should focus on maternal cousins, uncles, and the grandfather. Some rare platelet function disorders (eg, Glanzmann thrombasthenia) and clotting factor deficiencies (eg, FXIII deficiency) are autosomal recessive, and their incidence is increased in consanguineous unions. The common inherited bleeding disorders (eg, vWD and mild platelet function abnormalities) usually are inherited in an autosomal dominant pattern. However, even these more common bleeding disorders can have variable expression and may be more likely to manifest in females because of gynecologic and obstetric experiences (eg, postpartum hemorrhage).

IS THERE ANY UNDERLYING SYSTEMIC DISEASE OR DRUG EXACERBATING BLEEDING?

Acquired bleeding disorders should be considered in patients who have an underlying medical illness or are taking concurrent medications. A primary hemostatic defect may be attributed to medications that have well-known antiplatelet adverse effects (eg, aspirin and other nonsteroidal anti-inflammatory drugs [NSAIDs]), but many medications used to treat a variety of disorders can have unappreciated

effects on platelet function and should be investigated. Underlying medical disorders may cause a bleeding phenotype due to thrombocytopenia or uremia. A coagulation factor abnormality may be a manifestation of liver disease, vitamin K deficiency, or disseminated intravascular coagulation (DIC).

Laboratory Evaluation

An appropriate and reliable laboratory approach, encompassing first-line (screening) and second-line (specific) testing, is essential to screen, diagnose, and monitor patients who have bleeding diatheses (Fig. 2). The available clinical assays also can be grouped according to whether they evaluate components of primary hemostasis or coagulation factors.

CLINICAL ASSAYS FOR EVALUATING PRIMARY HEMOSTASIS.

A complete blood count and evaluation of the peripheral blood smear usually constitute the required first step. The bleeding time is the historical screening test for defects of primary hemostasis, but low sensitivity and specificity in children limit its utility. Newer platelet function analyzers (PFAs) are now available in clinical laboratories but cannot be relied on to identify all patients who have vWD or platelet function defects, and

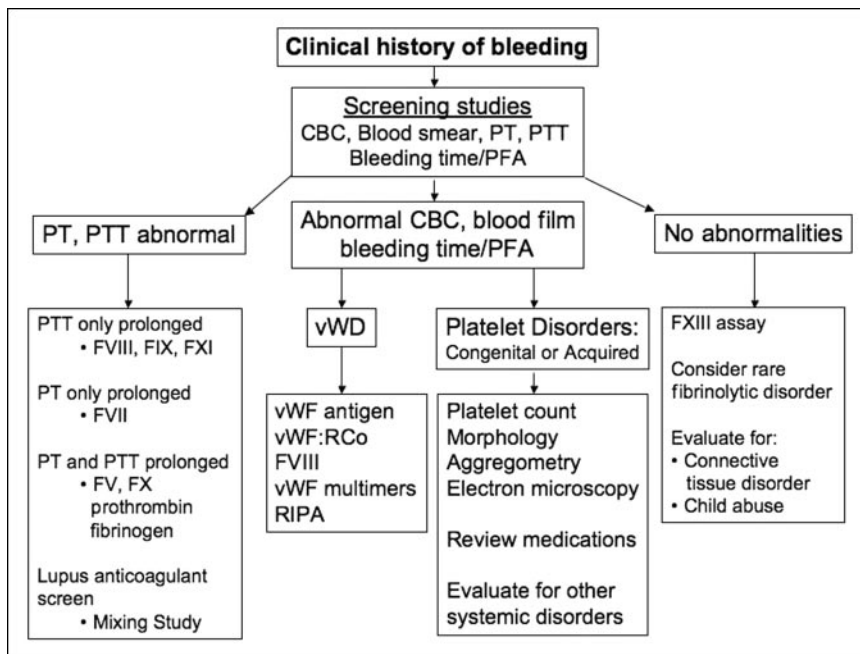


Figure 2. Laboratory evaluation of bleeding disorders. CBC=complete blood count, F=factor, PFA=platelet function analyzer, PT=prothrombin time, PTT=activated partial thromboplastin time, RIPA=ristocetin-induced platelet aggregation, vWD=von Willebrand disease, vWF=von Willebrand factor, vWF:RCo=ristocetin cofactor activity.

their routine use remains controversial. Therefore, when these disorders are considered, specific testing (vWF indices, platelet aggregation studies) should be performed.

CLINICAL ASSAYS FOR EVALUATION OF COAGULATION FACTOR FUNCTION. The prothrombin time (PT) and activated PTT are coagulation screening tests performed on citrated plasma. The PT is reported commonly along with the International Normalized Ratio (INR) to adjust for different reagent sensitivities. The PT is a measure of the extrinsic (FVII) and common pathway (FV, FX, prothrombin, fibrinogen) clotting factors. The PTT measures the contact system (prekallikrein, FXII) as well as the intrinsic (FVIII, FIX, FXI) and common pathway clotting factors. Sensitivities of various PT and PTT reagents vary and may yield normal values in the presence of mild factor deficiencies. Therefore, specific factor assays should be performed for patients who are strongly suspected of having a bleeding disorder. An understanding of the relationships among the PT; PTT; and the intrinsic, extrinsic, and common pathways helps guide additional specific factor assays (Fig. 2).

The terminal event for both the PT and PTT assays is the conversion of soluble fibrinogen to insoluble fibrin. Because neither of these tests assesses the activity of FXIII, a specific FXIII assay must be requested to prevent missing this rare but important coagulation factor deficiency.

Incidental detection of a prolonged PTT occurs commonly in the primary care setting; such prolongation often is found in children who have no history of bleeding. This finding usually can be attributed to a lupus anticoagulant (LA), antibodies that arise transiently, often in association with infections, and are directed against proteins that bind phospholipid surfaces. Despite marked prolongations of the PTT, such antibodies do not cause bleeding; paradoxically, they have been linked with some thrombotic complications in childhood. However, in most children, the LA antibodies are uncomplicated and disappear over several weeks, with an accompanying normalization of the PTT. Rarely, LA is associated with an antibody directed against prothrombin, which can lead to an accompanying prothrombin deficiency manifested by both a prolonged PT and PTT. This subgroup of affected patients can present with acute bleeding problems but also can exhibit a transient clinical course. LA can be confirmed by a mixing study in which patient plasma is mixed 1:1 with normal plasma and the PTT is measured. If a clotting factor deficiency is present, the PTT completely corrects to within the normal range.

However, in the presence of an LA, the PTT remains prolonged.

Normal reference ranges for the PT and PTT are wider in newborns, reflecting relative immaturity of the vitamin K pathway. Published reference ranges for coagulation assays for newborns of different gestational ages are available. Laboratory methods and standards differ among institutions; local age-matched reference ranges should be used when available.

Inherited Bleeding Disorders of Primary Hemostasis

von Willebrand Disease

vWD is the most common genetic bleeding disorder. It affects both sexes, and the prevalence is estimated to be as high as 1%. Three primary vWD types should be distinguished: type 1 (70% to 80% of cases) and type 3 (rare) are characterized by partial and virtually complete deficiency of vWF, respectively; type 2 vWD reflects a qualitative defect in vWF function (Table 1). Clinical presentations vary substantially, depending on the subtype and severity, and manifestations range from mild mucocutaneous bleeding to hemarthroses.

Due to the heterogeneity of vWF defects and external variables (such as blood group and other physiologic modifiers) that can influence vWF concentrations in the circulation, diagnosing vWD can be difficult. The bleeding time can be normal in affected patients. vWD is diagnosed most often if the patient satisfies three criteria: 1) a positive bleeding history, 2) reduced levels of vWF activity (ristocetin cofactor [RCo] activity), and 3) a positive family history suggestive of vWD. The vWF:RCo assay is the most useful tool for screening patients, but other assays are required to distinguish among the various subtypes. These other tests include vWF antigen, FVIII activity, vWF multimer analysis, ristocetin-induced platelet aggregation at low concentrations of ristocetin (seen with Type 2B), and blood typing.

Because vWF is an acute-phase reactant, concentrations increase with stress, exercise, acute inflammatory processes, and pregnancy and during the menstrual cycle. The plasma concentration of vWF also is modified by other determinants such as blood group and race. The plasma vWF antigen values for individuals who have type O blood are 25% lower than in pooled normal plasma, leading to a greater likelihood of diagnosis in those who have type O blood. In contrast, those who have type AB blood have concentrations averaging 25% higher than pooled plasma. African American women tend to have values 15% higher than white women. When clinical symptoms or family history suggest vWD, a single nega-

Table 1. von Willebrand Disease

Features	Type 1	Type 2A	Type 2B	Type 2N	Type 2M	Type 3
Defect	Partial quantitative deficiency with normal structure and function of vWF	Quantitative and qualitative defect with loss of HMW/M	↓ affinity of vWF to platelet membrane GP Ib/IX/V complex	↓ affinity of vWF for FVIII mimicking hemophilia A	Qualitative defect with retention of HMW/M	Complete deficiency of vWF
Pattern of bleeding	Mucocutaneous	Mucocutaneous	Mucocutaneous	Mucocutaneous, soft tissue, joint	Mucocutaneous	Mucocutaneous, soft tissue, joint
Inheritance	AD	AD	AD	AR	AD	AR
Bleeding time and/or PFA-100	N or ↑	↑	N or ↑	N	N or ↑	↑
Platelet count	N	N	N or ↓	N	N	N
Factor VIII activity	N or ↓	N or ↓	N or ↓	↓ (discrepantly low compared to vWF antigen)	N or ↓	Markedly ↓
vWF Antigen*	↓	↓	N or ↓	N	N or ↓	Markedly ↓
Ristocetin cofactor activity (vWF:RCO)*	↓	↓	N or ↓	N	↓ (discrepantly low compared to vWF antigen)	Markedly ↓
Ristocetin-induced platelet aggregation with low dose of ristocetin	Absent	Absent	Present	Absent	Absent	Absent
vWF multimer analysis	N	Absence of HMW/M	Absence of HMW/M	N	N	Absent
Response to DDAVP	Good	Variable	Worsening of thrombocytopenia	Good vWF response; poor FVIII activity response	Variable	None

AD=autosomal dominant, AR=autosomal recessive, DDAVP=desmopressin acetate, HMW/M=high-molecular weight multimers, PFA=platelet function analyzer, vWF= von Willebrand factor, ↑ = prolonged, ↓ = decreased, N = normal
 *Laboratory interpretation of von Willebrand factor concentrations should be evaluated in the context of the patient's blood group

tive test does not rule out the diagnosis; repeated laboratory measurements often are needed.

Two primary options are available to treat spontaneous bleeding episodes and for bleeding prophylaxis: desmopressin (DDAVP) and transfusional therapy with plasma-derived vWF products. DDAVP is the treatment of choice for most patients who have type 1 vWD and a subset of patients who have types 2A and 2M vWD. This hemostatic agent raises endogenous vWF plasma concentrations two- to fourfold and causes a similar rise in FVIII activity. Because peak values can be achieved within 1 hour after administration, the agent is useful for surgical prophylaxis.

Prior to considering DDAVP for treatment, a DDAVP challenge test should be performed by measuring vWF indices before and after the administration of DDAVP. The dose of DDAVP is 0.3 mcg/kg for intravenous use and 150 to 300 mcg via the intranasal route. DDAVP can be safely administered daily for several days in a row. The major adverse effects associated with its use include facial flushing, headache, tachycardia, and hyponatremia. Due to the risk of hyponatremic seizures, DDAVP should be used with utmost caution in young children (<2 y of age) and children undergoing surgical procedures associated with significant blood loss. Simultaneous use of antifibrinolytic agents (ε-aminocaproic acid, 50 mg/kg q 6 hours; tranexamic acid, 25 mg/kg q 4 to 6 hour) helps to stabilize the clot by preventing plasmin-mediated clot lysis.

For patients who have the more severe type 3 and in most patients who have type 2 disease, DDAVP is ineffective or is contraindicated, usually necessitating the use of plasma concentrates containing both FVIII and vWF. Virally inactivated products always should be used rather than cryoprecipitate. These agents are dosed in vWF:RCo units (1.5% plasma increase for every 1 IU/kg infused). vWF-containing concentrates also should be considered for patients whose disease is mild and who have failed to have their bleeding controlled with DDAVP or antifibrinolytic agents. Adolescent girls presenting with menorrhagia as their primary bleeding manifestation may have bleeding controlled with oral contraceptives as well as DDAVP.

Platelet Function Disorder

Thrombocytopenia is another important cause of bleeding manifestations in children, but the approach to this problem is beyond the scope of this review. Platelet function disorders may be congenital or acquired and commonly present with spontaneous mucocutaneous bleeding or bleeding after hemostatic challenge (eg,

trauma, surgery). Acquired disorders are most common. Antiepileptic medications (eg, valproate) and antidepressants can cause functional impairment of platelets. Antiplatelet agents such as aspirin cause platelet inhibition for the entire life span (~5 to 7 d) of the platelet; other NSAIDs inhibit platelets as long as the drug is present. Systemic disorders such as uremia, congenital heart disease, liver failure, and leukemia also can lead to platelet function defects. Any possible acquired causes for platelet dysfunction should be ruled out before an inherited cause is considered.

Congenital platelet disorders are less common and are comprised of inherited defects in receptors critical to platelet adhesion and aggregation, defects in signaling molecules that impair platelet secretion, and defects in platelet metabolism. The clinical presentation is variable but usually manifests with mild mucocutaneous bleeding. Patients in whom the disorders are suspected may be screened *in vivo* for a prolonged bleeding time or *ex vivo* using a PFA. Platelet aggregometry tests platelet aggregation and secretion responses to a variety of agonists. Some disorders exhibit structural abnormalities under light or electron microscopy.

The bleeding symptoms in hereditary platelet disorders often can be ameliorated with DDAVP and antifibrinolytic agents, although certain severe disorders (eg, Bernard-Soulier syndrome and Glanzmann thrombasthenia) may require platelet transfusions. Recently, recombinant FVIIa (rFVIIa) has been shown to be effective in controlling bleeding in patients who have these more severe platelet function defects. Such use of this agent has not been approved yet by the United States Food and Drug Administration.

Congenital Deficiency of Coagulation Proteins

Hemophilia

Hemophilia A and B result from deficiency or dysfunction of FVIII or FIX, respectively. The incidence of hemophilia A is estimated to be 1 in 5,000 male births and that of hemophilia B is estimated at 1 in 30,000 male births. Because the genes for both FVIII and FIX are located on the X chromosome, hemophilia primarily affects males, although females may be symptomatic carriers. All the female offspring of an affected male are obligate carriers. Carrier females have a 50% chance of passing the affected chromosome to their male offspring. Clinical severity, corresponding factor concentrations, and clinical signs are elaborated in Table 2. The typical presentation is excessive bleeding after circumcision. However, with fewer families choosing circumcision, this

Table 2. Clinical Classification of Hemophilia

Classification	Severe	Moderate	Mild
FVIII or FIX activity	<1%	1% to 5%	6% to 30%
Frequency	50% to 70%	10%	30% to 40%
Cause of bleeding	Spontaneous	Minor trauma, rarely spontaneous	Major trauma, surgery
Frequency of bleeding	2 to 4 times/mo	4 to 6 times/y	Uncommon
Pattern of bleeding	Joint, soft tissue, bleeding after circumcision, neonatal intracranial hemorrhage	Joint, soft tissue ± bleeding after circumcision, ± neonatal intracranial hemorrhage	Joint, soft tissue, ± bleeding after circumcision

early bleeding challenge often is missed. Later presentations in infancy can include severe mucosal bleeding from tongue or gum injuries and prominent bruising, with hematomas over both the trunk and extremities. The classic bleeding manifestations of severe hemophilia, severe soft-tissue bleeding and hemarthroses, typically do not begin until the child becomes ambulatory, mostly after the first birthday.

Those who have hemophilia usually have a prolonged PTT, with normal PT, platelet count, and bleeding time/PFA testing. The diagnosis is confirmed by analysis of FVIII or FIX activity. FVIII activity already is at “adult” values at birth. However, because FIX is a vitamin K-dependent factor, FIX concentrations typically are low in the newborn period. Follow-up FIX activity should be measured after 4 to 6 months of age to confirm a diagnosis of mild hemophilia B. Mild reductions in FVIII also should prompt measurement of vWF concentrations to rule out vWD.

Patients who have hemophilia can be treated with episodic or prophylactic infusions of factor concentrates. In developed countries, most children who have severe hemophilia are treated with prophylactic therapy to prevent the chronic complications associated with frequent joint bleeding and to prevent life-threatening bleeding. Much of the treatment is home-based after the parents, caregivers, and eventually the patient learn venipuncture technique.

Due to concerns about transfusion-transmitted diseases in the past and an increasing demand for factor concentrates worldwide, most pediatric patients in the developed world now are treated with recombinant-derived FVIII and FIX concentrates. Recombinant FVIII concentrates produce a 2% rise in plasma FVIII concentration for every 1 IU/kg infused. Current recombinant FIX concentrates produce about an 0.8% rise in plasma FIX concentration for every 1 IU/kg infused. Target replacement should aim for a 50% correction of

the plasma value for most hemorrhages. However, replacement for major hemorrhages (head and neck, abdominal, intracranial) should aim for 100% plasma values. Perioperative management always should be conducted in consultation with a pediatric hematologist.

Following treatment with FVIII concentrates, up to 30% of patients who have hemophilia A develop antibodies (called inhibitors) against FVIII, usually within the first 50 exposures. The incidence of inhibitors is lower in hemophilia B (1% to 3%). Most inhibitors are detected during routine surveillance, but such antibodies may seriously complicate the treatment of bleeding events or surgery if the inhibitor emerges during the treatment. Patients who have inhibitors usually are unresponsive to factor concentrates but can be treated with “bypassing” agents, such as rFVIIa or activated prothrombin complex concentrates.

The care of patients who have hemophilia within a network of specially trained hemophilia treatment centers has greatly reduced the mortality and morbidity once associated with this condition. Patients whose disease is severe now can expect a lifespan similar to that of healthy males who have little to no joint disease as adults.

Prenatal diagnosis options for women known to be carriers for hemophilia include: 1) noninvasive fetal sex determination by ultrasonography and 2) invasive testing by chorionic villus sampling or amniocentesis for specific diagnosis. Due to the greatly enhanced quality of life with current hemophilia therapy, most women currently opt for noninvasive fetal sex determination facilitated by ultrasonography in the second trimester. This allows for appropriate decisions regarding delivery options and accelerated diagnostic testing in the newborn period.

Rare Congenital Bleeding Disorders

Additional rare congenital coagulation bleeding disorders that have autosomal recessive inheritance include deficiencies/dysfunction of coagulation factors V, VII,

X, XI, XIII, and fibrinogen. Affected patients present with prolongations of the PT or PTT or both, with the exception of FXIII, as mentioned earlier. In addition, there are rare inherited disorders of fibrinolysis in which patients exhibit excessive fibrinolytic activity that compromises clot stability. Clinicians should consider a connective tissue disorder (eg, Ehlers-Danlos syndrome) if significant mucocutaneous bleeding is accompanied by normal laboratory study results.

Acquired Bleeding Disorders

The most common causes of bleeding encountered in clinical practice are due to acquired systemic disorders. Abnormal hemostasis in liver disease involves a variety of mechanisms, including impaired hepatic synthesis, activation of both coagulation and fibrinolytic systems, loss of hemostatic proteins into ascitic fluid, concurrent vitamin K deficiency, thrombocytopenia, and platelet dysfunction. Management of coagulopathy due to hepatic dysfunction should include replacement of coagulation factors with fresh frozen plasma (FFP) or cryoprecipitate, vitamin K replacement, and platelet transfusions.

Acquired vitamin K deficiency should be suspected in chronically ill children who have malabsorption syndromes such as cystic fibrosis, biliary atresia, and celiac disease. Hemorrhagic disease of the newborn (HDN) is attributed to hepatic immaturity in the synthesis of vitamin K-dependent clotting factors. Generally, affected infants have been delivered at home and have not received prophylactic vitamin K injections. HDN can be treated with intramuscular or oral vitamin K. Uremia and cardiopulmonary bypass and extracorporeal membrane oxygenation circuits can cause bleeding through both qualitative and quantitative platelet defects. In addition, during cardiopulmonary bypass, the concentrations of both coagulant proteins and inhibitors of coagulation decrease significantly due to hemodilution. These disorders can be treated with FFP and platelet transfusions. DDAVP can aid in improving bleeding symptoms in children who have renal failure. However, close monitoring of fluid and electrolyte balance is required to avoid hyponatremia in this population.

DIC is a consumptive coagulopathy that involves simultaneous activation of coagulation and the fibrinolytic system. This presentation most often is accompanied by prolongations of coagulation screening tests, thrombocytopenia, and elevated concentrations of fibrin degradation products (eg, D-dimer). In addition to pro-

viding supportive therapy through replacement of coagulation factors with FFP and platelets, correction of the underlying cause (sepsis, malignancy, trauma) is the primary aim of management.

Acquired inhibitors to coagulation proteins such as FVIII or FIX are rare in children. Acquired vWD has been reported in children who have congenital heart diseases with right-to-left shunt due to rapid clearance of large vWF multimers. For children who have Wilms tumor, adsorption of vWF on malignant cells can lead to acquired vWD.

Coagulopathy in children who have acute promyelocytic leukemia has been shown to be associated with DIC. Treatment with FFP, platelets, and antifibrinolytic agents may be required to control bleeding in such patients.

Summary

The general pediatrician remains the “front line” for the identification of congenital and acquired bleeding disorders. Prompt and accurate diagnosis is critical to ensure timely and appropriate therapy and to avoid potentially life-threatening complications. Detection involves a careful and focused history and physical examination as well as diagnostic screening studies. Knowledge of available therapies is helpful in emergent situations, even when a rare disorder is suspected. A pediatric hematologist should be consulted once patients are identified to aid in diagnosis and to recommend long-term management.

Suggested Reading

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Useful Web Sites

National Hemophilia Foundation: www.hemophilia.org/resources/handi/htm

Safety checklist for young children: <http://parentcenter.babycenter.com/general/72315.html>

PIR Quiz

Quiz also available online at www.pedsinreview.org.

6. Which of the following clinical features is *most* likely to be associated with a benign condition?
 - A. Bleeding 7 days after a tonsillectomy.
 - B. Bruises over the bony prominences of the extremities, both proximal and distal.
 - C. Epistaxis (worse in winter).
 - D. Hemarthrosis.
 - E. Menstrual bleeding that lasts 8 days.

7. Which of the following coagulation factors is measured exclusively by the activated partial thromboplastin time?
 - A. Factor V.
 - B. Factor VII.
 - C. Factor VIII.
 - D. Factor X.
 - E. Factor XIII.

8. You are evaluating a 15-year-old girl who has had heavy periods since menarche at age 13 years. Her periods are regular, but she experiences heavy bleeding that lasts for 8 to 9 days with each cycle. She denies other bleeding. Her mother reports a similar menstrual history. Her physical examination findings are normal. Laboratory evaluation reveals a normal platelet count, prothrombin time, and partial thromboplastin time with a normal bleeding time. Of the following, which is the *most* likely diagnosis in this patient?
 - A. Bernard-Soulier syndrome.
 - B. Factor VIII deficiency.
 - C. Hemophilia B.
 - D. Systemic lupus erythematosus.
 - E. von Willebrand disease.

9. A 3-year-old boy comes to your office with a limp. He reports falling while playing tag with his brother earlier that day. His medical history is unremarkable except for prolonged bleeding after circumcision. There is no family history of bleeding. His physical examination reveals a tender, large, bluish mass in the left quadriceps muscle, which his mother says has enlarged quickly over the last few hours. You suspect a bleeding disorder. Of the following, which is the *most* likely bleeding disorder in this patient?
 - A. Acute lymphoblastic leukemia.
 - B. Factor XIII deficiency.
 - C. Hemophilia A.
 - D. Immune thrombocytopenic purpura.
 - E. von Willebrand disease.

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