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Hemophilia: In Review

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Author Disclosure
Dr Zimmerman has disclosed no financial relationships relevant to this commentary. Dr. Valentino has disclosed he is a consultant and on the advisory board of Baxter Healthcare Corp., Bayer HealthCare Pharmaceuticals, Biogen Idec, CSL Behring, GTC Biotherapeutics, Inspiration Bioscience, NovoNordisk, and Pfizer, for which Rush University receives grant support and honoraria payments. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gap

General pediatricians rarely encounter bleeding in a neonate or a child, so it is important to know the genetics of hemophilia and to be aware of the clinical manifestations of bleeding disorders in order to appropriately identify those children at risk, ensure early diagnosis and treatment, and prevent complications.

Objectives

After completing this article, readers should be able to:

1. **Describe the coagulation system and the basic physiology of blood clotting.**
2. **Know the genetics of hemophilia and be able to estimate the relative risk of hemophilia in carriers of the mutation.**
3. **Discuss the clinical manifestations and the potential complications of hemophilia.**
4. **List the initial laboratory studies needed to evaluate children who have bleeding.**
5. **Understand the role of comprehensive care in the treatment of patients with hemophilia.**

Hemophilia A (deficiency in factor [F] VIII) and hemophilia B (deficiency in FIX) are the most common serious congenital coagulation factor deficiencies. Hemophilia A is more common, occurring in 1:5000 male births, whereas hemophilia B occurs in 1:30,000 male births. Hemophilia is found in all ethnic groups; there is no geographic or racial predilection. Although easy bruising and excessive mucosal bleeding may be the first signs of hemophilia, severe soft tissue bleeding and hemarthroses are the classic bleeding symptoms. Other bleeding disorders should be considered when evaluating a child with unexpected bleeding. Factor deficiencies (FV, FVII, FX, FXI, FXIII, and fibrinogen) may present with bleeding or abnormal coagulation laboratory test results. von Willebrand disease is caused by a deficiency in von Willebrand factor (VWF), which is released from endothelial cells at the site of vascular injury. Because there are 3 subtypes (which are different in both severity and heredity), clinical symptoms vary from mild mucosal bleeding to hemarthroses. If a bleeding disorder appears to be acquired, nutritional deficiencies (especially vitamin K) or associated illnesses (disseminated intravascular coagulation or liver disease) should be considered. Platelet disorders, either quantitative or qualitative defects, present with mucocutaneous bleeding. In the evaluation of a suspected platelet disorder, medications and systemic diseases that affect platelet function should also be considered.

Abbreviations

a: activated
F: factor
PT: prothrombin time
PTT: partial thromboplastin time
TF: tissue factor
VWF: von Willebrand factor

Basics in Bleeding and Clotting

The primary function of the coagulation system is to maintain the integrity of the endothelium while preserving vasculature patency. The basal state of the coagulation system is nonthrombogenic for 2 main reasons: the coagulation factors circulate in their inactivated forms and the endothelium is nonthrombogenic. Disruption of the endothelium causes exposure of the thrombophilic subendothelium and initiation of the hemostatic mechanism. The classic pathway of coagulation has been replaced by a cell-based model of coagulation (Figure 1) in which tissue factor (TF), platelets,

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and thrombin play key roles in initiating, amplifying and propagating clot formation.

Hemostasis involves the complex interaction of platelets with the vessel wall mediated primarily by collagen in low-shear (venous) and VWF in high-shear (arterioles) circuits, both serving an adhesive function in bridging platelets to the subendothelium, where the coagulation proteins dock to phospholipid sites on the surface of activated platelets, resulting in fibrin-generating concentrations of thrombin.

Coagulation is typically triggered after the exposure of TF, found in the subendothelium, which binds circulating activated (a) FVII. The TF-FVIIa complex activates zymogen FX and FIX to FXa and FIXa, respectively. FXa converts prothrombin (FII) to thrombin (FIIa). The picomolar quantities of FIIa generated on the TF-bearing cell surface releases FVIII from its carrier protein VWF and activates it to FVIIIa. Thrombin also activates platelets, exposing a negatively charged phospholipid-rich surface capable of binding coagulation proteins, including FIXa, previously generated on TF-bearing cell surface. FIXa along with cofactor FVIIIa, calcium, and phospholipids form the Tenase complex, recruit FX to the complex, and activate it to FXa. FXa along with calcium and phospholipids form the prothrombinase complex, which in turn converts large quantities of prothrombin to thrombin, such that fibrinogen is converted to fibrin monomers. Thrombin also activates FXIII, which cross-links the fibrin monomers to stabilize the clot, and thrombin-activatable fibrinolysis inhibitor, which prevents clot breakdown, both improving clot firmness.

Theoretical consideration of the classic or waterfall view of coagulation is useful in interpreting the results of prothrombin time (PT) and partial thromboplastin time (PTT) used as screening tools to evaluate patients with hemorrhage or a tendency for hemorrhage (Table 1). The intrinsic system consists of FXII and FXI, which along with high-molecular-weight kininogen and prekallikrein form the contact pathway, and FVIII and FIX. The extrinsic system is composed of TF and FVII. The common pathway includes FX, FV, thrombin, and fibrinogen.

Genetics

The genes encoding FVIII and FIX are on the long arm of the X chromosome. Hemophilia A and B are the only hereditary clotting diseases inherited in a sex-linked recessive pattern. All female children of a father with hemophilia will be carriers, whereas none of his sons will be affected. Further, the sons of a carrier mother have a 50% chance of disease, whereas the daughters will have a 50% chance of being a carrier (Figure 2).

The genetic mutations cause a quantitative decrease in protein expression, a qualitative decrease in protein activity, or both. Approximately 5% to 10% of patients with hemophilia A and 40% to 50% of patients with hemophilia B make a dysfunctional protein, which results in decreased protein activity without a quantitative decrease. More than 1000 mutations in either the factor 8 or factor 9 genes have been identified to cause clinical hemophilia. There is a high rate of spontaneous mutation (approximately one-third of cases) such that even in the absence of a family history, hemophilia should be suspected in a newborn with bleeding and a prolongation in the PTT. Through lyonization of the X chromosome, females with Turner syndrome or X chromosomal mosaicism may have bleeding disorders secondary to reduction in either FVIII or FIX activity.

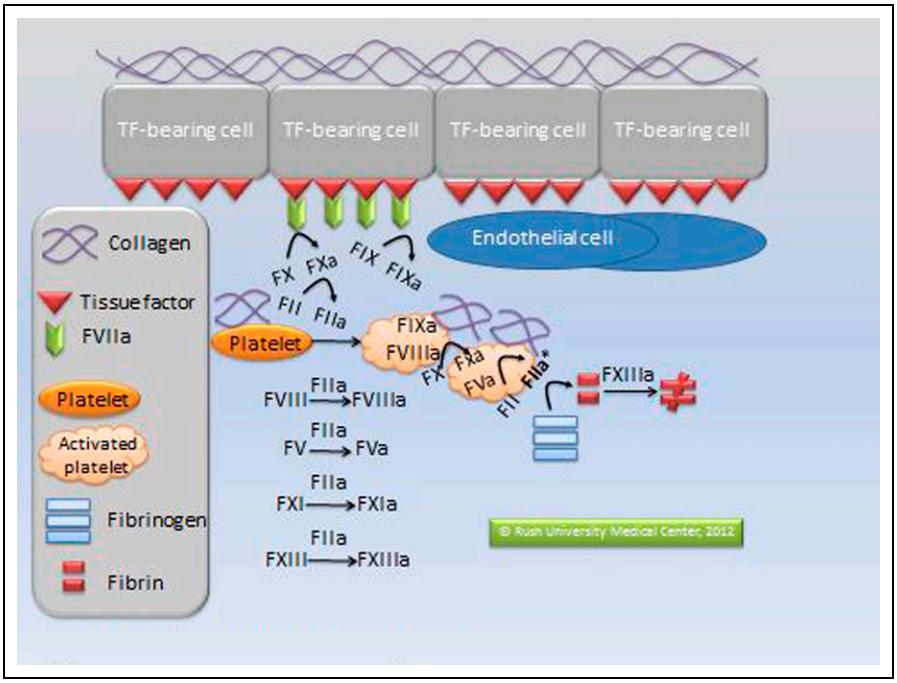

Figure 1. Cell-based model of blood coagulation. F=factor; TF=tissue factor.

Table 1. **Interpretation of Screening Tests of Coagulation**

Increased PT With Normal PTT	Normal PT With Increased PTT	Increased PT and Increased PTT
Deficiency of FVII[a]	Deficiency of FXII, FXI, FIX, or FVIII	Deficiency of FX, FV, FII, or FI
Inhibition of tissue factor	Inhibitor of FXI, FIX, or FVIII	Inhibitor of FX, FV, FII, or FI
	Lupus anticoagulant	Heparin
	Heparin	

F=factor; PT=prothrombin time; PTT=partial thromboplastin time.
[a]Congenital or vitamin K dependent.

Pathophysiology

The reduced level or activity of FVIII or FIX results in dysfunctional clotting. In patients without hemophilia, FVIIIa and FIXa associate on the surface of activated platelets and form the Tenase complex, which leads to the formation of thrombin and subsequently a fibrin clot. Because both FVIIIa and FIXa are required for Tenase formation, the clinical manifestations when either factor is dysfunctional are the same.

Disease Classification and Clinical Features

Disease classification is based on the residual factor level, which correlates to bleeding symptoms (Table 2). By convention, the percentage activity of each of the factors is based on the World Health Organization standard. By this standard, 1 mL of normal plasma has 1 IU/dL of each factor activity. Normal plasma is thought to have 100% activity, but in reality the lower limit of normal for individuals without hemophilia is 50%. Mild hemophilia is defined by greater than 5% to 40% factor activity, which correlates to major trauma or surgery required for bleeding. Moderate hemophilia has 1% to 5% factor activity, and mild trauma or surgery may induce bleeding. Severe hemophilia, in which spontaneous bleeding often occurs, correlates to less than 1% factor activity.

The clotting factors responsible for hemophilia do not cross the placenta; therefore, bleeding may occur in utero, although this is rare. In the neonatal period, 50% of male infants with severe hemophilia will bleed excessively with circumcision. Pediatricians who encounter a male newborn with bleeding, in particular after phlebotomy or at the time of circumcision, should consider a diagnosis of hemophilia. The occurrence of intracranial hemorrhage should most certainly result in exclusion of hemophilia as an underlying cause. Most patients with severe hemophilia (90%) will present in the first year of life, especially while learning to cruise or walk. Excessive bruising and intramuscular hematomas are common, but bleeding into a joint space, or hemarthrosis, is the hallmark of hemophilia. The following large joints, in order of decreasing frequency, are most often involved: knees, elbows, ankles, shoulders, wrists, and hips. Older children describe a burning or tingling sensation preceding other physical stigmata of hemarthrosis (warmth, major swelling, pain, or limited range of motion). If treated appropriately, pain usually decreases within

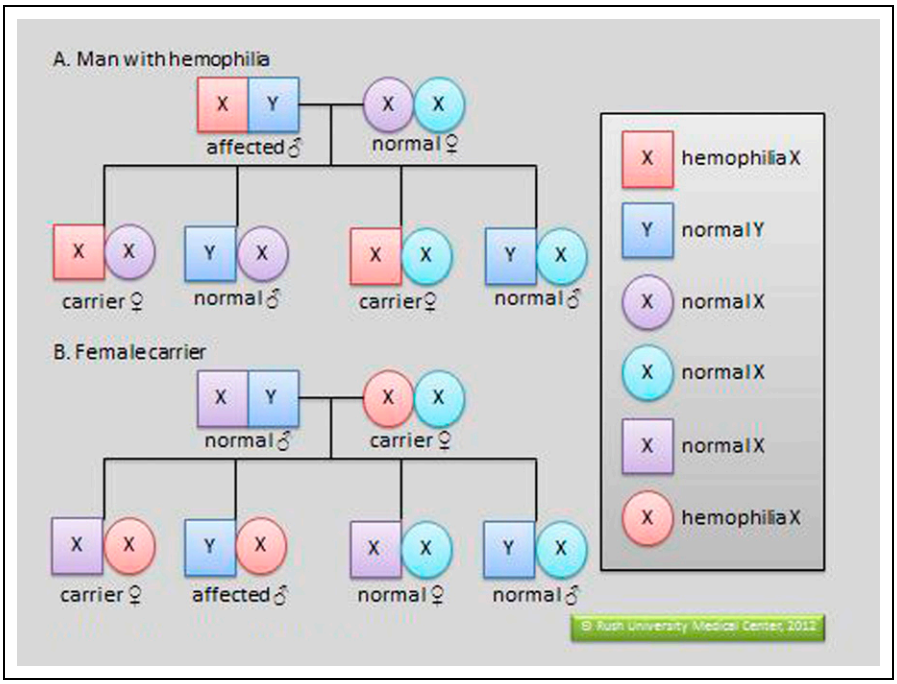

Figure 2. Inheritance of hemophilia.

Table 2. Relationship of Factor Activity to Clinical Bleeding

Severity	Activity, %	Cause of Bleeding
Mild	>5	Significant trauma or surgery
Moderate	1–5	Mild trauma or surgery
Severe	<1	Spontaneous trauma or surgery

8 to 12 hours. Recurrent hemorrhage into a particular joint or "target joint" often develops.

Although any type bleeding is possible in hemophilia, 3 life-threatening areas are important to consider. The first type is an intracranial hemorrhage, which is the leading cause of death in patients with hemophilia. Although intracranial bleeding may be spontaneous, it usually follows trivial trauma. Any patient with hemophilia and suspected intracranial bleeding should be treated before undergoing any diagnostic testing. The second type is bleeding into the iliopsoas muscle. Massive bleeding may occur with bleeding in the iliopsoas muscle with few symptoms. Referred vague pain to the groin may be reported, whereas physical examination will reveal a hip that is flexed and internally rotated. Because such large volumes of blood may be lost into the retroperitoneum without significant symptoms, life-threatening hypovolemic shock may occur. Lastly, bleeding may occur in the neck when the retropharyngeal space is expanded by a hematoma, occluding the airway.

Laboratory Findings

Prolongation of the PTT is found in hemophilia, whereas the PT, bleeding time, and thrombin time will all be normal. In severe hemophilia the PTT will be 2 to 3 times longer than the reference range. In a mixing study, when the plasma of the patient with hemophilia is mixed with normal plasma (which contains all the factors for clotting) the PTT should normalize. If the PTT does not normalize during a mixing study, suspicion is raised for an inhibitor (see the Complications section), and a Bethesda assay may be performed to quantify the inhibitor.

Prenatal diagnosis is available via chromosomal analysis of cells obtained by amniocentesis or chorionic villus sampling. Although prenatal testing is not routinely offered, identification of a male fetus in the context of a carrier family is a good opportunity for genetic counseling.

Management

Factor replacement is needed for treatment of bleeding in hemophilia. Early factor replacement is the standard of care. Factor can be administered during an episode of bleeding (on-demand therapy) or in a prophylactic manner in the absence of bleeding.

Prophylaxis or lifelong treatment with factor to prevent spontaneous bleeding is the optimal treatment plan for patients with severe hemophilia. Evidence from a large randomized controlled trial suggests that prophylactic treatment (vs episodic treatment) prevents hemarthroses and joint damage (see the article by Manco-Johnson et al). The primary outcome of joint disease is important because coexisting arthropathy is a chronic debilitating disease in patients with hemophilia, leading to chronic pain, limitations in function, and reduced quality of life. Despite the clear benefit of prophylaxis for severe hemophilia, this treatment has significant barriers. In fact, recent surveying of hemophilia treatment centers proved that fewer than half of patients with severe hemophilia A are being treated with the recommended prophylaxis schedule as delineated by the Medical and Scientific Advisory Council of the National Hemophilia Foundation.

Table 3. Factor Therapy for Acute Bleeding

Type of Hemorrhage	Goal Level of Factor, %	Dose of Factor VIII,[a] U/kg
Renal	50	25
Laceration	50–100	25–50
Joint	40–60	20–30
Muscle (superficial)	40–60	20–30
Gastrointestinal		
Initial	80–100	40–50
Maintenance	50	25
Ophthalmic		
Initial	80–100	40–50
Maintenance	>50	25
Iliopsoas		
Initial	80–100	40–50
Maintenance	>50	25
Throat/neck		
Initial	80–100	40–50
Maintenance	>50	25
CNS		
Initial	80–100	40–50
Maintenance	>50	25
Surgery (major)		
Initial	80–100	40–50
Maintenance	>50	25

CNS=central nervous system.
[a]Doses of factor IX are typically twice those of factor VIII because the in vivo recovery after intravenous injection of factor VIII is typically 2% infused in contrast to factor IX, which is closer to 1% infused.

Specific guidelines on the optimal time to initiate prophylaxis, dosing of factor concentrate, and the length of treatment are not universally accepted; often therapy will differ among treatment centers. Ideally, prophylaxis is initiated before repeated hemarthroses occur. Factor is generally given 1 to 4 times per week via central catheter or peripheral venipuncture. It is recommended that trough levels of factor activity and inhibitor development are monitored several times per year. Cost is a significant barrier to wide acceptance of prophylaxis in the United States. Each unit of recombinant FVIII costs essentially $1; therefore, the cost of prophylaxis for a child weighing 50 kg is $300,000 per year. For comparison, the median pharmaceutical costs for an on-demand regimen may be as low as $50,000 annually. The presence of an inhibitor may increase the pharmaceutical costs to close to $1 million annually. Of note, these values do not take into account health care costs for chronic disease or surgical procedures, both of which are decreased with prophylactic factor treatment.

During acute bleeding, factor is give to raise activity based on the severity of the hemorrhage (Table 3). In a life-threatening hemorrhage, factor is initially infused to a target activity of 80% to 100%, whereas in mild to moderate bleeding the goal is factor activity of 35% to 50%. Maintenance doses are generally given every 12 hours in hemophilia A and every 24 hours in hemophilia B. The duration of the dosing is dependent on the location and severity of bleeding and the response of the patient.

Desmopressin is also used for treatment of bleeding in mild to moderate hemophilia A. Desmopressin is most conveniently administered intranasally but is also administered intravenously or subcutaneously. The precise mechanism of action is unknown, but factor VIII levels may increase 2- to 3-fold above baseline, with a peak response 30 to 60 minutes after dosing. Not all patients will respond; response should be determined before bleeding episodes. Of note, response decreases with repeated administration (tachyphylaxis) during a short period. Desmopressin is a synthetic analogue of vasopressin, which causes conservation of water in the kidney. Fluid intake must be restricted to avoid the hyponatremia with excessive water intake.

Surgery represents a major bleeding risk for patients with hemophilia. Before major surgery factor activity is raised to normal levels. Factor is administered by repeated bolus injection or continuous intraoperative infusion, and levels are maintained at a normal level for 1 to 2 weeks afterward to promote wound healing. Aminocaproic acid and tranexamic acid are lysine analogues that act as competitive inhibitors of plasminogen. These can be used for clot stabilization after surgical interventions.

Complications

Before the 1980s factor concentrates were prepared from thousands of donors and pooled. The contamination with virus of pooled preparations was common. Patients with hemophilia were at risk for acquiring blood-borne disease, especially human immunodeficiency virus and hepatitis B and C. Starting in 1985 the pooled factor preparations have been treated with heat or solvent detergent, which led to the elimination of the viral contamination risk. Decades ago, the leading cause of death in patients with

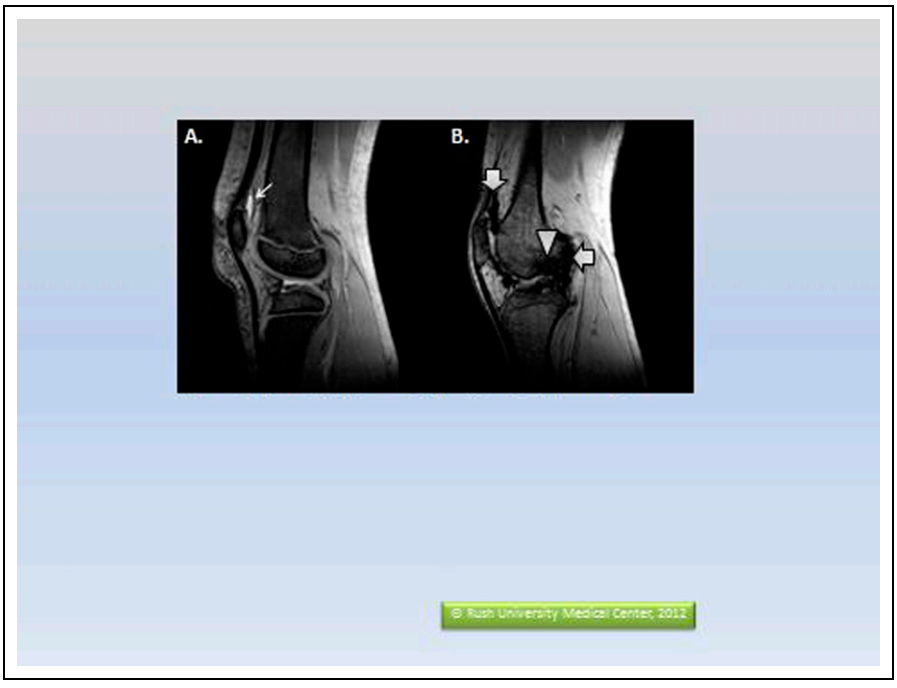

Figure 3. Magnetic resonance images (MRIs) of the knee. A. Normal MRI of the right knee. The arrow indicates a small effusion. B. Abnormal MRI of the right knee. There is hemosiderin-laden synovial hyperplasia (arrows) extending into the central joint space. There are subchondral cysts (triangle) and destruction of the articular cartilage. There is marrow edema within the patella and a subpatellar effusion.

hemophilia was AIDS or chronic liver disease, whereas now a patient with hemophilia is expected to have a lifespan approaching that of individuals without hemophilia.

The most serious iatrogenic complication of hemophilia treatment today is the development of factor inhibitors. Inhibitors are specific antibodies (IgG) that develop against factor VIII or IX preparations. These immunoglobulins cause the neutralization of the infused factor. Inhibitors are more common in hemophilia A, developing in up to 30% of patients. In hemophilia B incidence is approximately 5%. During the first 50 exposures to factor, patients are most likely to develop inhibitors, correlating to a mean age of 1 to 2 years at onset. Those with large deletions, severe disease, and early exposure to factor and family history of inhibitors are at the greatest risk.

Repeated hemarthroses lead to chronic arthropathy, joint deformity, muscle atrophy, and soft tissue contractures. Hemoglobin released from erythrocytes becomes deposited into affected joint spaces and subsequently leads to an inflammatory synovitis. With each joint hemorrhage, the synovium thickens further. Subsequent bleeding into a joint causes destruction of the bone and cartilage. Joint surface disease is often identified by early childhood, and debilitating arthropathy is present by adolescence (Figure 3). Primary prevention of arthropathy can be achieved via treatment with factor prophylaxis. Hemarthrosis in a previously unaffected joint is managed aggressively with factor replacement, splinting, physical therapy, and close follow-up. However, once arthropathy is present, surgical intervention is often required. Synovectomy, joint debridement, joint fusion, and joint arthroplasty are commonly performed to manage joint disease.

Comprehensive Care Clinics

Nationwide, hemophilia treatment centers have been established to improve access to care for patients with hemophilia to a multidisciplinary group of health care professionals. The health care team generally consists of hematologists, orthopedists, physical therapists, nurses, social workers, pharmacists, psychologists, dentists, and registered dieticians. Prevention of complications is a major goal of hemophilia treatment centers, and in fact, patients who receive care at a comprehensive care clinic are 40% less likely to be hospitalized for bleeding complications.

Summary

- **Hemophilia A (deficiency in factor [F] VIII) and hemophilia B (deficiency in FIX) are the most common serious congenital coagulation factor deficiencies. (Based on strong evidence)**
- **Hemophilia is a genetic disorder inherited in an X-linked fashion. Both diseases cause similar bleeding diatheses, with the hallmark being hemarthroses. (Based on strong evidence)**
- **The optimal treatment is recombinant factor replacement to prevent bleeding; however, this treatment has many barriers. (Based on strong evidence)**
- **The most serious complication of treatment is the development of inhibitors to factor products. (Based on strong evidence)**
- **Care for patients with hemophilia is most appropriate in a comprehensive care setting. (Based on strong evidence)**

Suggested Reading

Heyworth BE, Su EP, Figgie MP, Acharya SS, Sculco TP. Orthopedic management of hemophilia. *Am J Orthop.* 2005; 34(10):479–486

Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med.* 2007;357(6):535–544

Mannucci PM, Tuddenham EG. The hemophilias—from royal genes to gene therapy. *N Engl J Med.* 2001;344(23): 1773–1779

Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al; Treatment Guidelines Working Group on Behalf of The World Federation of Hemophilia. Guidelines for the management of hemophilia. *Haemophilia.* 2013;19(1):e1–e47

Valentino LA, et al. Healthcare resource utilization among haemophilia A patients in the United States. *Haemophilia.* 2011; (Nov):1–7

Parent Resources From the AAP at HealthyChildren.org

The reader is likely to find material relevant to this article to share with parents by visiting these links:

- http://www.healthychildren.org/English/health-issues/conditions/treatments/Pages/Blood-Transfusion-Options.aspx
- http://www.healthychildren.org/English/health-issues/conditions/treatments/Pages/Are-Blood-Transfusions-Safe-for-Children.aspx

PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

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In *Pediatrics in Review*, *AMA PRA Category 1 Credit™* may be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. A mother is a carrier for hemophilia. Which of the following is true regarding chance of carrier state for her offspring, assuming her husband does not have hemophilia?
   A. Her daughters will have a 50% chance of being a carrier.
   B. Her daughters will have a 75% chance of being a carrier.
   C. Her daughters will have a 100% chance of being a carrier.
   D. Her sons will have a 50% chance of being a carrier.
   E. Her sons will have a 75% chance of disease.

2. A newborn male with bleeding and a prolonged partial thromboplastin time (PTT) has no family history of a bleeding disorder. What percentage of children with hemophilia has the disorder in absence of a family history?
   A. 10% of cases.
   A. 25% of cases.
   C. 33% of cases.
   D. 50% of cases.
   E. 75% of cases.

3. Bleeding into a joint space is the hallmark of hemophilia. Which of the following joints are most often involved?
   A. Ankles.
   B. Elbows.
   C. Hips.
   D. Knees.
   E. Shoulders.

4. What is the leading cause of death in patients with hemophilia?
   A. Circumcision bleeding.
   B. Iliopsoas muscle bleeding.
   C. Intracranial bleeding.
   D. Retropharyngeal space bleeding.
   E. Target joint bleeding.

5. Which of the following therapies is most effective for prophylaxis to prevent hemarthrosis and joint damage in patients with hemophilia?
   A. Aminocaprioc acid.
   B. Desmopressin.
   C. Plasma infusion.
   D. Recombinant factor.
   E. Tranexamic acid.

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