Hemophilia: The Past, the Present, and the Future

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PRACTICE GAPS

General pediatricians are usually not familiar with the treatment and management of patients with bleeding disorders. Hemophilia is the most common severe coagulation factor deficiency. Early recognition of this condition and adequate understanding of its management are of extreme importance to prevent treatment- and condition-specific complications that lead to the development of chronic disabilities in children. Pediatricians must be aware of the role that comprehensive hemophilia treatment centers play for these patients and the need to establish a multidisciplinary model as the gold standard for hemophilia management.

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

1. Describe the pathophysiology of hemophilia.
2. Know the genetics of hemophilia and its relative risk of transmission.
3. Identify the clinical signs and symptoms associated with hemophilia.
4. Understand the basics of hemophilia treatment and the most common long-term complications.
5. Recognize the role of the hemophilia comprehensive care centers in the management of patients with hemophilia.

OVERVIEW

Hemophilia A and B are inherited bleeding disorders characterized by the partial or complete deficiency of circulating coagulation factors VIII (FVIII) or IX (FIX), respectively. The hallmark of severe hemophilia is the presence of recurrent, spontaneous, prolonged, and abnormal bleeding episodes primarily involving soft tissues and synovial joints.

Hemophilia A, or classical hemophilia, has been described since ancient times. The earliest documentation is found in the Talmud, a collection of Jewish law

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ABBREVIATIONS

aPTT	activated partial thromboplastin time
FVII	coagulation factor VII
FVIII	coagulation factor VIII
FIX	coagulation factor IX
FX	coagulation factor X
HTC	hemophilia treatment center
ICH	intracranial hemorrhage
ITI	immune tolerance induction
POC-MSKUS	point-of-care musculoskeletal ultrasonography
TFPI	tissue factor pathway inhibitor
VWD	von Willebrand disease
VWF	von Willebrand factor
WFH	World Federation of Hemophilia

writings, from the fourth century. These manuscripts state that infant boys were exempt from the covenant of circumcision if 2 previous sons from the same mother had died due to severe bleeding associated with the procedure. (1) In 1803, John Conrad Otto was the first physician to report a hemorrhagic disorder, characterized by joint and muscle bleeds, that exclusively affected males in the same family. It was not until 1828 that Friedrich Hopff, a student at the University of Zurich, and his professor, Dr Schonlein, used the term *haemorrhaphilia* for patients presenting with this constellation of symptoms. (1)

Hemophilia has often been called "the royal disease" because several members of the European royal family were affected by the condition. Queen Victoria of England, the most famous hemophilia carrier, passed the condition to several of her own children, spreading the disorder to other European royal families. The most renowned case is Tsarevich Alexei, son of the Russian Czar Nicholas II. Today, we know that this royal disease was in fact hemophilia B. Hemophilia B is also known as Christmas disease after Stephen Christmas, the first person described with the condition in 1952. (1)

EPIDEMIOLOGY

Hemophilia A is 4 times more common than hemophilia B, comprising 80% of all hemophilia cases. The estimated prevalence of hemophilia A is approximately 1 in 5,000 male live births (2)(3) and of hemophilia B is 1 in 30,000 male live births. Hemophilia affects all ethnic and racial groups. A recent meta-analysis estimated that there are approximately 1,125,00 males living with hemophilia worldwide, of whom approximately 418,000 have severe hemophilia. (4)(5)(6) It has also been reported that in the United States the prevalence of severe disease is approximately 50% for patients with hemophilia A compared with approximately 30% for patients with hemophilia B. (7)(8)(9)

PATHOPHYSIOLOGY

Abnormal bleeding can occur when specific components of the hemostatic system are missing or dysfunctional. Hemostasis is the sequential and self-regulated physiologic process beginning as soon as a tissue or blood vessel injury occurs. Normal hemostasis produces formation of a stable platelet-fibrin clot that stops bleeding while maintaining normal blood flow. Vasoconstriction at the site of vessel injury is the initial step. This is followed by "primary hemostasis," when an initial, but unstable, platelet clot gets formed through the adhesion, activation, and aggregation of platelets on the damaged vascular endothelium. Primary hemostasis relies on an adequate quantity of functionally normal von Willebrand factor (VWF). Stabilization of the platelet plug through the formation of a covalently cross-linked fibrin-platelet clot occurs during "secondary hemostasis." Secondary hemostasis consists of the activation of all coagulation factors in the coagulation cascade (Fig 1). Within the cascade, FVIII and FIX form an enzymatic complex with coagulation factor X (FX), producing activated FX, which ultimately induces a "thrombin burst," facilitating the formation of the fibrin-platelet clot.

Regulation of the hemostatic process occurs through fibrinolysis. Fibrinolysis consists of dissolving the formed clot after the wound-healing process is completed, thereby preventing the formation of a thrombus in otherwise normal blood vessels. Components of the fibrinolytic system include antithrombin, tissue factor pathway inhibitor (TFPI), protein C, and protein S. (10)

In hemophilia, a partial or complete deficiency of either FVIII or FIX will result in decreased formation of fibrin, causing a bleeding diathesis characterized by recurrent and prolonged bleeding episodes. (11) FVIII or FIX levels are expressed either as a percentage of normal activity or as international units per deciliter. The reference range for both factors fluctuates between 50% and 150% (0.50–1.50 IU/dL).

GENETICS

Hemophilia is inherited in an X-linked recessive pattern. Males are predominantly affected because they have only a single X chromosome, which expresses the defective gene. Affected males can transmit the disease-causing gene only to their female offspring, designated "obligate carriers." Hemophilia carriers have one normal and one abnormal FVIII or FIX gene and have a 50% chance of transmitting the gene to any child; males inheriting the hemophilia gene express the disease, and females become hemophilia carriers (Fig 2).

Carrier females might or might not manifest low factor levels and symptoms. Mild hemophilia can be present in up to 25% of heterozygous female carriers. (2) Infrequently, females can manifest a severe bleeding phenotype. This occurs in the context of a compound heterozygous female born from a father with hemophilia and a hemophilia carrier mother. A female carrier can also have hemophilia because of extreme lyonization of the normal X chromosome.

Since the FVIII gene was first described in 1983, different mutation variants in the FVIII and FIX genes have been identified. (7) The most frequent variants in patients with hemophilia A are the intron 22 and intron 1

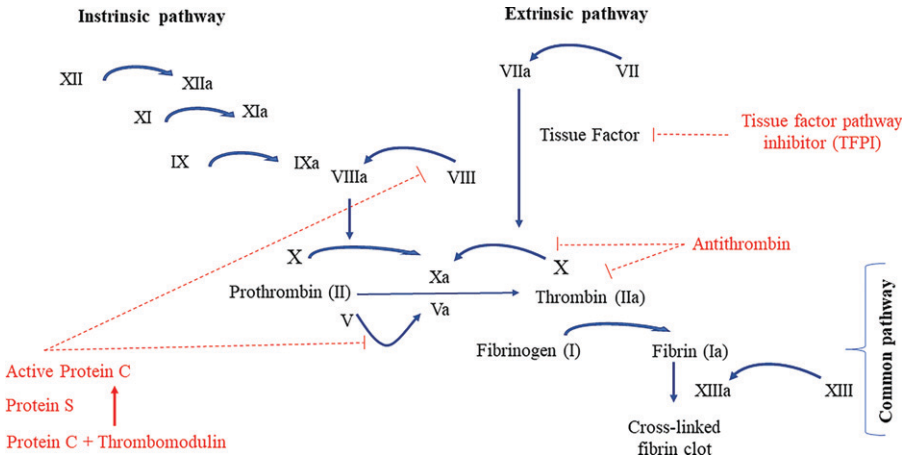

Figure 1. Coagulation cascade (secondary hemostasis).

inversions. The former is identified in close to 52% of patients with severe hemophilia A, whereas the latter is encountered in 1% to 5% of all patients with hemophilia A. The most common genetic variants identified in hemophilia B are missense mutations, which account for approximately 47% of all cases. (12) The "My Life, Our Future" project was established in 2012 with the goal of creating a repository of genetic information from people with hemophilia in the United States. FVIII of FIX gene sequence analysis was offered at no cost to patients with hemophilia and suspected carriers. In 2018, an interim analysis identified 700 previously unreported genetic variants and reclassified as nondeleterious several variants previously reported as causative hemophilia mutations. (13)

CLINICAL MANIFESTATIONS

Hemophilia is classified as mild, moderate, and severe based on the measurable factor activity level (Table 1). There is a direct correlation between FVIII or FIX levels and the severity and relative frequency of patient signs and symptoms. Patients with severe and moderate deficiencies tend to present symptoms in the first months after birth. (2)(14)(15) It has been suggested that patients with hemophilia B seem to have less severe bleeding signs and symptoms and better long-term outcomes than patients with hemophilia A. (16)

Because neither FVIII nor FIX crosses the placenta, bleeding signs and symptoms in persons with hemophilia, especially those with severe forms, can present soon after birth; in some instances, bleeding can even occur in utero. In infants, intracranial hemorrhage (ICH) occurring either during birth or shortly thereafter is a significant concern. The use of forceps during delivery and vacuum extraction are considered high-risk factors for the development of ICH. The overall incidence of ICH at birth in newborns with hemophilia is estimated to be 4% to 5%, although cases of spontaneous ICH have also been reported. (17)

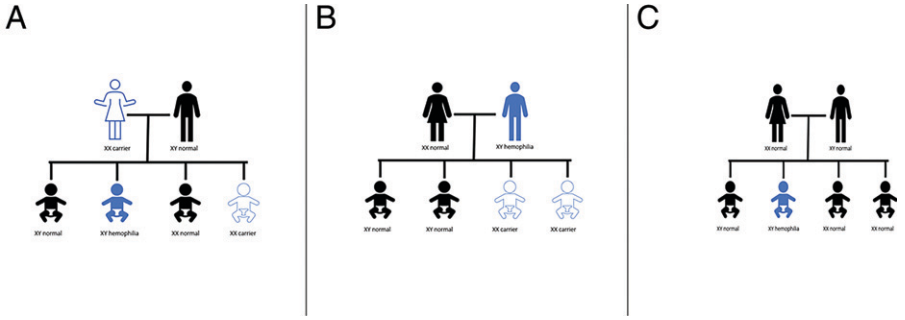

Figure 2. Inheritance patterns of hemophilia. A. Mother carrier of hemophilia gene, father does not have hemophilia. B. Father has hemophilia and mother does not carry hemophilia gene. C. An example of spontaneous mutation, neither father nor mother has hemophilia.

Table 1. Hemophilia Severity

	MILD HEMOPHILIA	MODERATE HEMOPHILIA	SEVERE HEMOPHILIA
Factor level, %	6–40	1–5	<1
Cause of bleeding	Major surgery, trauma	Minor trauma, not commonly spontaneous	Spontaneous
Average age at diagnosis (11)	>3 y	3 mo	1 mo
Bleeding pattern	Joint, soft tissue ± bleeding after circumcision, bleeding with surgical procedures	Joint, soft tissue ± bleeding after circumcision ± neonatal intracranial hemorrhage, bleeding with surgical procedures	Spontaneous joint and soft tissue, bleeding after circumcision, neonatal intracranial hemorrhage, bleeding with surgical procedures

ICH also needs to be considered in cases of head trauma, such as an infant falling from a crib or bed. When suspecting an ICH in a child with hemophilia, immediate infusion of factor concentrate before a head computed tomographic scan is indicated and should not be delayed.

The hallmark of hemophilia bleeding is the occurrence of spontaneous acute hemarthrosis. Acute hemarthrosis is defined as the sudden onset of bleeding into the joint space, accompanied by joint swelling, pain, and reduced range of motion of the affected joint. Ankles, knees, and elbows are the most frequently affected joints. The clinical manifestations of joint bleeding vary depending on the patient's age and are sometimes challenging to recognize by medical providers. Infants can present with irritability and unwillingness to use the affected limb. Older children and adults can present with prodromal symptoms characterized by a warm or tingling sensation or feeling of fullness and stiffness of the affected joint before onset of the more characteristic swelling and reduced range of motion. Point-of-care musculoskeletal ultrasonography (POC-MSKUS) is becoming a preferred imaging modality for both the acute assessment and management of joint bleeds (Fig 3) and for monitoring of the development and progression of subclinical joint disease. As opposed to other imaging modalities such as magnetic resonance imaging, POC-MSKUS is less invasive, does not require sedation, is less time-consuming, and has been found to be exceptionally sensitive in detecting very low amounts of intra-articular blood. (18)(19) At the moment, multiple hemophilia-specific POC-MSKUS scoring systems have been developed and are in different stages of validation. (19)

When more than 4 bleeding episodes occur in the same joint in a 6-month period, the patient is considered to have developed a "target joint." Repetitive bleeding in the joint space causes a chronic inflammatory reaction, characterized by a cytokine-mediated oxidative process and iron deposition, resulting in vascular proliferation, synovial hypertrophy, and chronic synovitis. Chronic synovitis will trigger an irreversible and destructive process known as hemophilic arthropathy.

Muscle bleeding with subsequent hematoma formation is also common in persons with hemophilia. Large muscles, such as the iliopsoas or quadriceps, are most commonly affected. Patients with muscular bleeding can

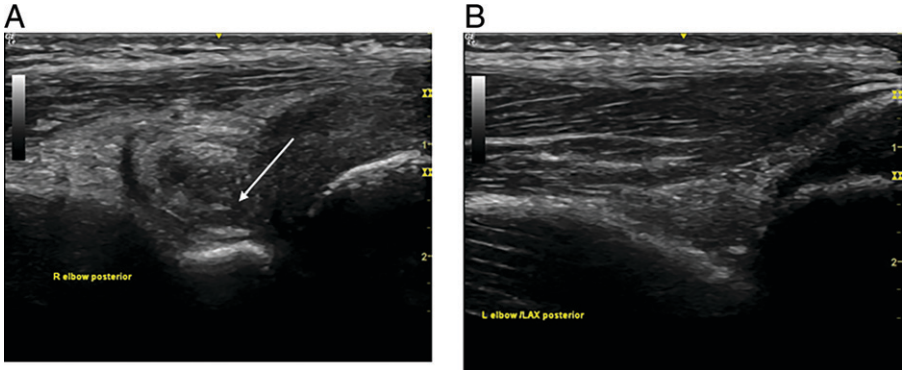

Figure 3. Point-of-care musculoskeletal ultrasonography used to detect an acute hemarthrosis in patients with hemophilia. A. Longitudinal posterior view of a right elbow demonstrating a heterogeneous, hyperechoic effusion (arrow) consistent with acute hemarthrosis. B. Longitudinal posterior view of the contralateral elbow with no signs of joint bleeding.

present with mild and nonspecific signs and symptoms: an iliopsoas bleed can manifest as vague groin pain and an inability to extend the hip. If the provider is suspicious for a psoas bleed, imaging confirmation with magnetic resonance imaging or POC-MSKUS is indicated.

Extensive muscle bleeding might result in a compartment syndrome, affecting neurovascular structures. Large amounts of blood loss in muscle can lead to pseudotumor formation. Hemophilic pseudotumor is a rare complication, occurring in 1% to 2% of patients with severe hemophilia. (1) A pseudotumor is a chronic, slowly expanding, encapsulated cystic mass that evolves after recurrent hemorrhages in extra-articular musculoskeletal structures.

Another bleeding site is the gastrointestinal tract. Patients with bowel hematomas can have signs and symptoms mimicking an acute abdomen. (20) Hematuria, secondary to bleeding arising from the kidneys or the bladder, is a frequent manifestation in persons with hemophilia, especially those with severe deficiencies. (21) Bleeding related to tooth eruption is rare. Dental care is extremely important in persons with hemophilia. Medical providers should promote early consistent dental hygiene practices to reduce the risk of development of periodontal disease. Preventive dental care (dental cleanings) should occur regularly. Dental extractions can require referral to an inpatient setting.

Carriers or women with mild hemophilia are also at risk for abnormal reproductive uterine bleeding associated with their menstrual period and childbirth. They can also face bleeding challenges during surgery or dental extractions. (22)

DIAGNOSIS

A complete family history exploring possible manifestations of bleeding in other family members is essential for the evaluation of a patient suspected of having hemophilia. Given the known genetic etiology of the disorder, questions about extended family members can prove enlightening. Depending on the studied population, 30% to 50% of patients with hemophilia will be found to have a sporadic de novo mutation. These patients are born to a noncarrier mother with a negative family history. For this reason, pediatricians should always consider the possible diagnosis of hemophilia in any male newborn with severe and unusual bleeding and an isolated prolonged activated partial thromboplastin time (aPTT) despite a negative family history of hemophilia. (23)

When hemophilia is suspected, the initial laboratory evaluation should include a complete blood cell count, prothrombin time, aPTT, mixing studies in case of prolonged aPTT, a fibrinogen level, and a VWF antigen and activity level.

Children with hemophilia present with an isolated prolonged aPTT and a normal platelet count and prothrombin time/international normalized ratio. Patients with severe hemophilia usually have an aPTT 2 or 3 times higher than the upper limit of normal. Unless the patient has an active inhibitor to FVIII or FIX, the aPTT mixing study will correct with the addition of normal plasma. Some cases of mild hemophilia can present with a normal aPTT due to poor sensitivity of the assay in the setting of mildly reduced FVIII or FIX levels. It is not possible to determine the severity of a hemophilia solely on the degree of prolongation of the aPTT. A specific assay to quantify the activity levels for FVIII or FIX will not only confirm the diagnosis but will help to differentiate other inherited bleeding disorders, such as deficiencies of coagulation factors XI or XII, which are also associated with an isolated prolonged aPTT. (24) Genetic testing is an important part of the hemophilia diagnostic evaluation. In addition to allowing accurate genetic counseling, some recognized mutations are associated with the potential risk of inhibitor development, the most common and severe complication of hemophilia treatment today.

Newborn males born to a known hemophilia carrier should have their factor level quantified at the time of delivery using a cord blood sample. Cord blood testing is preferred over venipuncture because the collection of cord blood minimizes the risk of traumatic bleeding. Invasive procedures, such as circumcision, should be delayed until the diagnosis of hemophilia is confirmed or eliminated. In babies confirmed to have hemophilia whose parents request a circumcision; the procedure should be electively performed by an experienced surgeon in collaboration with the hemophilia treatment center (HTC).

Patients with mild hemophilia might not be diagnosed until adolescence or early adulthood in the setting of surgical or dental procedures. Abnormal and excessive bleeding will lead to the diagnosis.

Ascertaining a hemophilia carrier's baseline factor activity is important for management, but if normal, it does not rule out the carrier's status. Genetic testing is more reliable than measurement of factor levels, especially in a woman with normal or borderline normal factor activity. Accurate identification of hemophilia carriers is important for managing current bleeding symptoms and troubleshooting potential bleeding complications associated with pregnancy and delivery. Knowledge of carrier

status allows appropriate recommendations for testing offspring. (2) Women with suspected hemophilia should also be tested for von Willebrand disease (VWD), as VWD variants or severe type 3 VWD can have a bleeding phenotype similar to that of hemophilia.

HEMOPHILIA MANAGEMENT

Traditionally, clotting factor replacement has been the standard of care for hemophilia. (25)(26) However, hemostatic adjuvant therapies are also helpful in controlling acute bleeding episodes.

Factor Replacement Therapies

Treatment of hemophilia has evolved significantly (Fig 4). In the 1950s and 1960s, bleeding events were treated with whole blood, fresh frozen plasma, or cryoprecipitate. Individuals with severe hemophilia experienced prolonged hospitalizations with bleeding events and developed significant joint morbidity. The 1970s brought the development of plasma-derived factor concentrates. In the 1980s through the early 1990s, contamination of these products with human immunodeficiency virus as well as hepatitis B and C devastated the hemophilia community. During that era, in the United States most individuals with hemophilia would treat bleeding events only on demand due to difficulties with an adequate supply of factor concentrates and concerns about factor concentrate safety. (27) In response to the human immunodeficiency virus and hepatitis epidemics, factor concentrate purity and safety became the therapeutic focus. Purification strategies for plasma-derived concentrates incorporated the development of enhanced blood donor screening and the development of techniques for viral removal and inactivation: pasteurization, solvent or detergent treatment, dry heating, immunoaffinity chromatography, and, more recently, nanofiltration. (28)(29)(30) These purification techniques have translated into no additional reports of viral transmission in patients using plasma-derived factor concentrates since the mid-1990s. (31) Today, safer recombinant factor concentrates are produced via transfection of the human FVIII or FIX gene in various cell lines, including the Chinese hamster ovary, baby hamster kidney, and human embryonic kidney. (31)(32)(33)(34)(35) Multiple generations of recombinant concentrates based on either the inclusion or exclusion of human or animal plasma-derived proteins are available. Standard half-life third-generation recombinant concentrates are commonly used in the United States. These concentrates contain neither human nor animal plasma-derived proteins in their cell culture media.

With the development of safer products, the treatment paradigm in hemophilia began to shift from treating bleeding episodes mainly on-demand to the use of prophylactic therapy: regularly scheduled administrations of factor concentrate to prevent bleeding events. Prophylaxis is defined as primary, secondary, or tertiary (Table 2). (26) Prophylaxis initiated early in life has been shown to provide superior benefits compared with on-demand episodic therapy. Early prophylaxis has been shown to result in a more than 90% reduction in joint bleeding rates and significant reductions in degenerative joint disease, hemophilic arthropathy, and potentially life-threatening bleeds. (36)(37) Preferred prophylactic regimens relying on standard half-life concentrates infuse FVIII at 25 to 40 IU/kg per dose every 2 to 3 days for patients with hemophilia A and

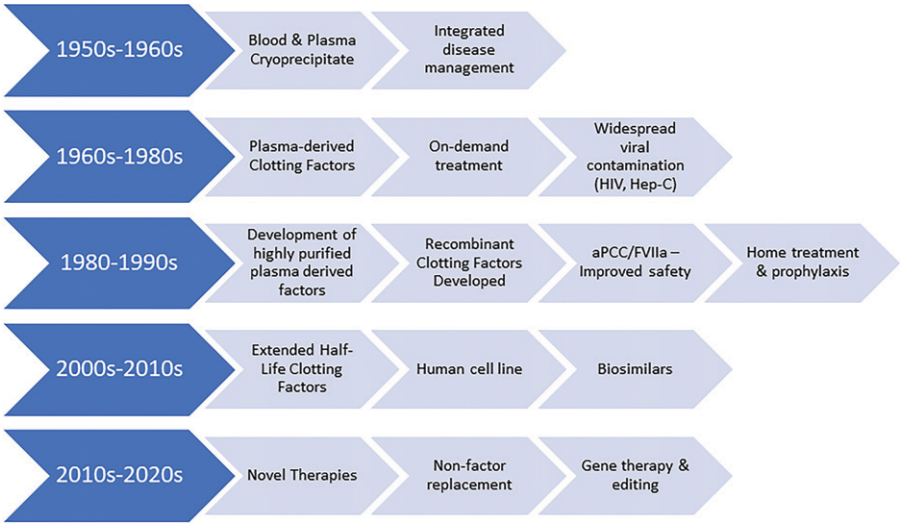

Figure 4. Evolution of hemophilia care.

Table 2. Types of Prophylaxis Regimens in Hemophilia

Primary prophylaxis	Regular, continuous prophylaxis that is begun in the absence of documented joint disease, before the second clinically evident joint bleed and before age 3 y
Secondary prophylaxis	Regular, continuous prophylaxis begun after ≥2 joint bleeds, before the onset of joint disease and typically ≥3 y
Tertiary prophylaxis	Regular, continuous prophylaxis begun after the onset of documented joint disease. It usually starts in adolescence or adulthood

FIX at 40 to 60 IU/kg twice weekly for patients with hemophilia B. An individualized regimen to prevent bleeding episodes is tailored to the individual needs of the patient. (26)(38)

Similar dosing can be used for breakthrough bleeding events, targeting factor levels of 80% to 100% or greater for management of critical bleeds, including intracranial, gastrointestinal, and iliopsoas bleeds. (26) It is recommended that preoperative factor levels greater than 50% to 100% are achieved depending on the specific procedure (Table 3). (26) Surgical hemostasis should be guided by an expert coagulation hematologist in coordination with the patient's local physician.

Factor dosing for acute bleeding episodes is calculated by multiplying the patient's weight (in kilograms) by the desired percentage of FVIII level; this total is then multiplied by 0.5 (volume of distribution) in patients with hemophilia A. For patients with hemophilia B, the total dose will equal the patient's weight (in kilograms) multiplied by the desired percentage of FIX level, multiplied by 1 (volume of distribution).

Table 3. Recommended Treatment Regimens for Acute Bleeding Episodes (26)

SEVERITY OF BLEEDING EPISODES	HEMOSTATIC FACTOR LEVEL REQUIRED (% NORMAL)	HEMOPHILIA A[a]	HEMOPHILIA B[b]	COMMENTS
Minor (early hemarthrosis, minor muscle or oral bleeding)	40%–60%	25–40 IU/kg every 12–24 h, as needed; if joint still painful after 24 h, treat for a further 2 d	40–60 IU/kg every 24 h as needed; if joint still painful after 24 h, treat for a further 2 d	For hemarthroses, use RICE (rest, immobilization, cold compresses, and elevation) For oral bleeding, antifibrinolytic therapy is critical
Moderate (hemarthrosis, significant muscle or oral bleeding)	60%–80%	Initial dose is 50 IU/kg. Then, 30–40 IU/kg every 12–24 h, as needed; for significant bleeding	Initial dose is 60–80 IU/kg. Then, 40–60 IU/kg every 24 h as needed; for significant bleeding	For iliopsoas bleeding, the treatment should continue for 10–14 d
Major (life- or limb-threatening hemorrhage, gastrointestinal bleeding, intracranial or intrathoracic bleeding, fractures)	Initial: 80–100% Maintenance: 30–60%	Initial dose is 50 IU/kg, then 25 IU/kg every 12 h (might need factor activity monitoring and dose adjustment in an inpatient setting)	Initial dose is 80–100 IU/kg, then 50 IU/kg every 24 h (might need factor activity monitoring and dose adjustment in an inpatient setting)	Treat presumptively before evaluation. Treatment should continue for 5–7 d
Hematuria	Painless and mild hematuria can be treated with complete bed rest and intense hydration (3L/m2 body surface area/day) for up to 48 hours. For persistent, painful and/or severe hematuria, required initial level is 100% and maintenance level is 40–60%	Initial dose is 50 IU/kg. If not resolved, 30–40 IU/kg every 12–24 h until resolved	Initial dose is 80–100 IU/kg. If not resolved, 30–40 IU/kg every 12–24 h until resolved	Avoid antifibrinolytics kg per day for 5–7 d)
Trauma or surgery	Initial: 100% Maintenance 40–60% until wound healing is complete	50 IU/kg; then 25 IU/kg every 12 h (might need factor activity monitoring and dose adjustment in an inpatient setting)	100 IU/kg; then 50 IU/kg every 24 h (might need factor activity monitoring and dose adjustment in an inpatient setting)	Evaluate for inhibitor before any elective surgery

[a]Hemophilia A dose calculation: the total dose equals the patient's weight (in kilograms) multiplied by the desired rise in factor VIII level, multiplied by 0.5 (volume of distribution).
[b]Hemophilia B dose calculation: the total dose equals the patient's weight (in kilograms) multiplied by the desired rise in factor IX level, multiplied by 1 (volume of distribution).

Routine vaccinations should be administered to children with hemophilia at age-appropriate intervals. The World Federation of Hemophilia (WFH) guidelines recommend administering these vaccines subcutaneously rather than intramuscularly. Ice should be applied to the site of injection for at least 5 minutes after vaccination, and pressure should be applied to the site for at least 10 minutes. (26) It is not recommended to administer factor concentrate before the administration of immunizations. For infants undergoing circumcision, it is recommended to increase the circulating factor VIII or IX levels to 80% to 100% before the procedure. The WFH guidelines also suggest the use of fibrin sealant as an adjunctive therapy.

As home-based prophylactic management of hemophilia has become routine, some patients have struggled to maintain adequate treatment adherence due to difficulty with venous access and time constraints. (39)(40)(41)(42)(43) This has led to the development of extended half-life factor concentrates focused on reducing treatment burden through decreasing the number of infusions required for prophylactic therapy. There have been recent extended half-life FVIII concentrates developed with different protein structures and manufacturing processes, including Fc-fusion and PEGylation, that demonstrate a modest prolongation of FVIII half-life. (44)(45)(46)(47) The approximately 1.5× half-life extension (48) allows twice weekly prophylactic dosing as opposed to 3 times per week or every other day infusions. This is due in part to the intimate interaction of factor VIII with VWF, its chaperone carrier protein in the circulation. (49) There might soon be a new class of FVIII concentrates that could further extend the FVIII half-life, leading to once weekly or even less frequent dosing. (50) Techniques to produce extended half-life FIX concentrates have been more successful in extending half-life using Fc-fusion, PEGylation, or albumin-fusion technologies. (51)(52)(53) These modifications have allowed prophylactic dosing every 7 to 14 days or longer. (54)

Nonfactor Replacement Therapies

The current hemophilia treatment paradigm has focused on replacing the specific deficient clotting factor to promote normal hemostasis. Several groups are investigating novel nonfactor therapies to either replicate the cofactor function of the deficient factor or modify the balance of coagulation proteins toward the prohemostatic.

Emicizumab is a humanized, monoclonal bispecific antibody developed to bind activated FIX and FX on the phospholipid membrane mimicking the FVIII cofactor functionality (Fig 5). (55)(56) Emicizumab is administered via subcutaneous injection, has a half-life of 4 to 5 weeks, and is approved for prophylaxis in individuals with hemophilia A with and without inhibitors. (56)(57)(58)(59) Due to its mechanism of action, emicizumab has the potential to induce severe adverse events such as thrombosis and thrombotic microangiopathy. (60) These adverse events have been particularly reported in individuals with hemophilia A and inhibitors who are concomitantly receiving emicizumab and activated prothrombin complex concentrate for breakthrough bleeding episodes. (60) Acute breakthrough, traumatic, or surgical bleeding in hemophilia A without inhibitors must be managed with infusions of FVIII concentrate because emicizumab is administered only for prophylaxis.

This first subcutaneous nonfactor therapy for hemophilia A is a breakthrough in patient convenience for prophylaxis. Note that the aPTT and 1-stage FVIII activity assays will not be accurate in the patient taking emicizumab because the traditional assays require activation of FVIII. Accurate FVIII

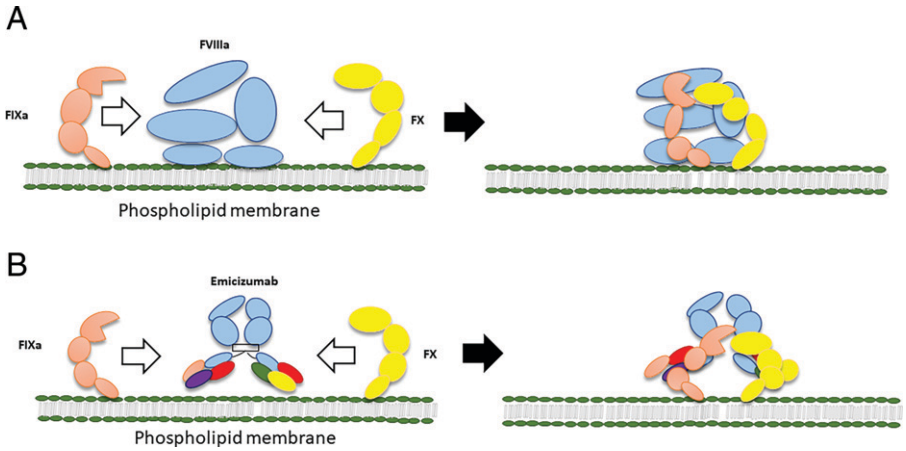

Figure 5. Emicizumab cross-linking. A. Factor VIII (FVIII) serves as a cofactor bringing together FIXa and FX. FVIII must be activated to FVIIIa before binding. B. Emicizumab, a humanized monoclonal antibody, binds activated FIXa and FX on the phospholipid membrane and mimics FVIII cofactor functionality.

activity requires the use of a bovine reagent factor VIII chromogenic assay should a patient taking emicizumab require concurrent administration of FVIII concentrate.

Other nonfactor therapies currently in development are based on the finding that some individuals with hemophilia and concurrent prothrombotic traits, such as antithrombin deficiency or factor V Leiden, have a milder bleeding phenotype. (61)(62) Fitusiran is an investigational, small interfering RNA engineered for suppression of antithrombin via posttranscriptional gene silencing in hepatocytes, thereby increasing the amount of thrombin generation. (63) This mechanism of action, however, creates a potential risk for development of thrombotic events. (64) Interim analysis from a phase 1 clinical trial reported a patient death associated with fitusiran involving the development of cerebral sinus thrombosis after concurrent FVIII concentrate administration. (65) The clinical trial resumed and recently reported positive long-term efficacy and safety data for the phase 2 extension study. (66)

TFPI is a Kunitz-type serine protease inhibitor that physiologically regulates excessive thrombin generation by inhibiting the tissue factor interaction with activated coagulation factor VII (FVII) and activated FX in the coagulation cascade. (67) Concizumab is an investigational, humanized, monoclonal antibody that blocks the physiologic regulatory action of TFPI, subsequently increasing thrombin generation in patients with hemophilia and healthy individuals. This therapy is currently undergoing clinical trials. (68)(69)(70) These studies were recently halted due to a few reports of nonfatal thrombosis, but clinical trials have since resumed. (71)

Additional, less developed nonfactor therapies, including inhibition of activated protein C or protein S, are currently under investigation. Recently, a serpin (serine protease inhibitor) was engineered to specifically inhibit the anticoagulant activities of activated protein C while preserving its other functions, restoring hemostasis in hemophilia mouse models. (72)(73) Another potential mechanism of activated protein C inhibition is via inhibitory monoclonal antibodies. (74) A small interfering RNA has also been developed in hemophilia mouse models to "silence" production of protein S, which can rebalance coagulation. (75) These nonfactor therapies under investigation can be additional avenues for future management.

Gene Therapy

A definitive cure for hemophilia has long been the dream of patients with hemophilia. (76) Hemophilia B saw the first success in the early 2010s with adenovirus-associated vector-mediated gene transfer, followed a few years later by hemophilia A. (77)(78)(79) The genetic material for the FVIII or FIX gene is packaged into a recombinant adenovirus capsid and is then infused via peripheral intravenous infusion. The viral vector with genetic material is then delivered to hepatocytes that become transfected and produce the deficient clotting factor. Through gene therapy, FVIII and FIX activities have been increased in patients with severe hemophilia to levels consistent with those found in mild hemophilia, or even normal hemostatic levels. A mild rise in transaminase levels occurring with gene transfection is typically transient. Patients are usually treated with a course of corticosteroids. Additional long-term safety encompasses potential adenoviral vector genome integration into the liver, although this occurs significantly less than with other viruses. (76)(80) Questions for gene therapy include long-term safety, efficacy, durability of response, and the appropriate therapeutic window. (76)(81)(82)

Hemostatic Adjuvant Therapies

Desmopressin, a synthetic analog of vasopressin, transiently increases the levels of FVIII and VWF, and it can be used to manage minor bleeding in patients with mild hemophilia A who have a documented response to this medication. Response is defined as a 2- to 3-fold increase above baseline FVIII levels, with a peak 30 to 60 minutes after dosing. Desmopressin is not effective in patients with severe hemophilia A and is not indicated in patients with hemophilia B. Desmopressin response decreases with repeated administration (tachyphylaxis), and it is usually contraindicated in children younger than 2 years due to its potential risk of dilutional hyponatremia and seizures.

Antifibrinolytic agents such as tranexamic acid and epsilon aminocaproic acid are helpful in controlling bleeding in areas with increased fibrinolytic activity, such as the oral mucosa and nasal cavity. They can be used in combination with factor replacement therapy to prevent bleeding associated with surgical procedures. These agents have also proved to be efficacious in controlling menorrhagia in women with mild hemophilia.

HEMOPHILIA-RELATED COMPLICATIONS

The classic major long-term complications of hemophilia are chronic hemarthroses with concomitant hemophilic arthropathy and the development of antibodies to infused coagulation factor concentrates (inhibitors). Because people with hemophilia are living longer, persons with

hemophilia are developing age-related comorbidities as well. Studies have shown a high incidence of obesity, cardiovascular disease, (83) and chronic kidney disease. (21) The increased bleeding risk in hemophilia and the lack of strong evidence-based guidelines for managing these comorbidities creates a higher risk of medical complications.

The development of inhibitors is the most severe complication of hemophilia treatment today. It remains a costly and important clinical challenge for the medical provider. Inhibitors are specific immunoglobulin G antibodies directed against FVIII or FIX that typically neutralize the activity of the infused factor. Inhibitors are reported to occur in approximately 35% of patients with severe hemophilia A and 5% of patients with severe hemophilia B. Inhibitors tend to develop within the first 50 exposure days, although most inhibitors will develop within the first 20 exposure days, correlating to a mean age of 1 to 2 years at onset. (15) Patients with moderate and mild hemophilia can develop inhibitors, but as young adults or older.

Several risk factors associated with an increased risk of inhibitor development have been identified. Severe hemophilia; specific genetic mutations, including large deletions and nonsense mutations; a family history of inhibitors; and African American and Hispanic background are known to be nonmodifiable and patient-specific risk factors for inhibitor development. (83) Environmental risk factors for inhibitor development include early age at first treatment exposure, type of concentrate (plasma-derived versus recombinant) used in treatment, dose intensity, and the use of prophylaxis versus on-demand treatment. Recently, the SIPPET study was the first large, prospective, and randomized trial investigating the differences in risk of inhibitor development between plasma-derived and recombinant factor concentrates in previously untreated children with hemophilia A. (84) Study results suggested that patients receiving recombinant concentrates are more likely to develop inhibitors than those receiving plasma-derived products. However, the study population was largely outside the United States, and study participants had an increased number of mutations associated with higher risk of inhibitor development. These results sparked a debate about the appropriate prophylactic regimen to initiate in newly diagnosed children with hemophilia. It is also important to realize that not all recombinant concentrates were included in the study, raising the question of whether these results could be generalized to all recombinant FVIII products, including newer standard and extended half-life concentrates.

The main therapeutic goal for patients with inhibitors is complete eradication of the antibodies. Immune tolerance induction (ITI) remains the most effective strategy for inhibitor eradication. It involves using high and frequent doses of factor concentrates to tolerize the patient's immune system to the factor and subsequently reducing the production of antibodies. Currently, the indications for ITI are individualized and depend on both the patient's clinical characteristics and preference. Emicizumab has recently become another option for patients with hemophilia A and inhibitors. Clinical studies have demonstrated high efficacy in preventing bleeding episodes when patients with hemophilia A with inhibitors are placed on emicizumab prophylaxis instead of on ITI, although these patients will still require a bypassing agent or high doses of FVIII concentrates to treat acute bleeding episodes. It is crucial for the medical provider to know the patient's inhibitor status and how to manage serious acute bleeding episodes in inhibitor-positive patients, including the use of bypassing agents such as recombinant activated FVII concentrate and activated prothrombin complex concentrates or the need for higher doses of FVIII (patients with hemophilia A) or FIX (patients with hemophilia B) concentrates.

HEMOPHILIA COMPREHENSIVE CARE

The 2020 WFH guidelines for the management of hemophilia state that a multidisciplinary comprehensive care model should be established when caring for individuals with hemophilia. Comprehensive HTCs have been established around the world. This treatment strategy ensures that persons with hemophilia have access to a full range of clinical specialties and appropriate laboratory services for the adequate management of their condition and associated complications. (26) In 1973, the National Hemophilia Foundation launched a 2-year campaign to establish the creation of a nationwide network of hemophilia diagnostic and treatment centers in the United States. To date, there are more than 140 HTCs across the nation. The establishment of this comprehensive approach during the past 40 years has greatly improved the quality of life not only for persons with hemophilia but also for all people with bleeding disorders, allowing them to live more independent and productive lives. A study of 3,000 persons with hemophilia showed that individuals treated at an HTC were 40% less likely to die of a hemophilia-related complication compared with those who did not receive care at an HTC. (8) Similarly, persons with hemophilia who used a treatment center were 40% less likely to be hospitalized for bleeding complications. (8)

Summary

- According to strong evidence, hemophilia A and B are the most common severe congenital coagulation factor deficiency disorders.
- According to strong evidence, hemophilia is a genetic disorder inherited in an X-linked recessive pattern, with hemarthrosis being the most common bleeding symptom.
- According to strong evidence, the clinical manifestations and bleeding phenotype in people with hemophilia depend on the residual activity level of factor VIII or IX.
- According to strong evidence, clotting factor concentrates remain the standard of care for prophylaxis and bleed management, but newer nonfactor therapies and gene therapy are making many therapeutic advances in the modern era.
- According to strong evidence, the treatment for hemophilia patients should occur in a comprehensive care setting at a hemophilia treatment center.

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References for this article can be found at http://pedsinreview.aappublications.org/content/42/12/672.

PIR QUIZ

1. An 18-year-old female, whose father has hemophilia B, is now pregnant. She has no history of bleeding symptoms. Which of the following is the most appropriate counseling regarding the hemophilia risk in her baby?

   A. If the baby is female, there is a 25% chance that she is a carrier.
   B. If the baby is female, there is a 100% chance that she is a carrier.
   C. If the baby is male, there is a 25% chance that he has hemophilia.
   D. If the baby is male, there is a 50% chance that he has hemophilia.
   E. If the baby is male, there is a 100% chance that he has hemophilia.

2. A 2-year-old boy with moderate hemophilia B presents after falling off a chair and hitting his head on the tile floor. There was no loss of consciousness. On physical examination he has a 3-cm raised hematoma on his forehead. Which of the following is the best initial management in this patient?

   A. Administer factor IX concentrate.
   B. Apply ice and topical fibrin.
   C. Check factor IX activity level.
   D. Obtain a computed tomographic scan of the brain.
   E. Request a neurosurgery consult.

3. A 9-month-old boy with severe hemophilia A presents with irritability and refusal to crawl. On physical examination there is no obvious swelling in the joints or muscles. Which of the following is the most likely cause of this patient's symptoms?

   A. Developmental delay.
   B. Hemarthrosis.
   C. Pseudotumor.
   D. Silent stroke.
   E. Synovial hypertrophy.

4. A 1-day-old boy is awaiting circumcision when the mother mentions that her father has hemophilia. Partial thromboplastin time on the infant is prolonged. Which of the following is the most appropriate course of action at this time?

   A. Administer factor VIII concentrate and perform circumcision.
   B. Consult pediatric surgery to perform circumcision.
   C. Refer to a hemophilia treatment center and postpone circumcision.
   D. Start emicizumab and schedule circumcision with urology.
   E. Transfuse fresh frozen plasma and perform circumcision.

5. A 12-month-old boy with mild hemophilia A has not yet received any vaccinations. The most appropriate approach to immunization in this infant is to administer which of the following?

   A. All vaccines but administered via the subcutaneous route.
   B. Factor doses before any vaccine administration.
   C. Factor doses before intramuscular vaccines only.
   D. No vaccines until factor prophylaxis is initiated.
   E. Only the vaccines that are intended for subcutaneous administration.

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