Chapter 123: Coagulation Disorders

Heidi Trinkman; Timothy L. McCavit; Lauren Duran

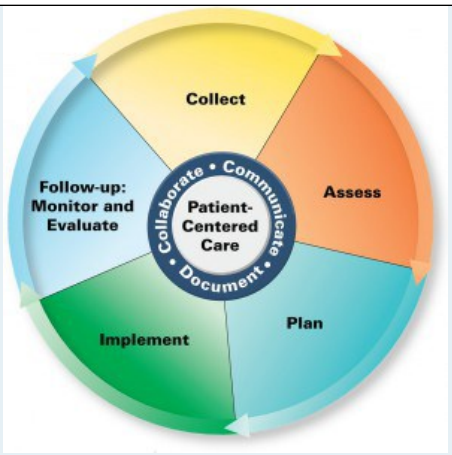
KEY CONCEPTS

KEY CONCEPTS

1. Hemophilia is an inherited bleeding disorder resulting from a congenital deficiency in factor VIII or IX.
2. The goal of therapy for hemophilia is to prevent bleeding episodes and their resulting long-term complications and to arrest bleeding if it occurs.
3. Recombinant factor concentrates usually are the first-line treatment of hemophilia because they have the lowest risk of infection.
4. Inhibitor formation is the most significant treatment complication in hemophilia and is associated with significant morbidity and decreased quality of life.
5. Recombinant factor VIIa is effective for the treatment of acute bleeds in patients with hemophilia A or B who have developed inhibitors.
6. The goal of therapy for von Willebrand disease (vWD) is to increase von Willebrand factor (vWF) and factor VIII levels to prevent bleeding during surgery or arrest bleeding when it occurs.
7. vWF concentrates are the agents of choice for treatment of type 3 vWD and some type 2 vWD, and for serious bleeding in type 1 vWD.
8. Desmopressin acetate often is effective for the treatment of type 1 vWD. It also may be effective for the treatment of some forms of type 2 vWD in addition to mild-to-moderate hemophilia A.

PATIENT CARE PROCESS

Patient Care Process for Coagulation Disorders



Collect

- Patient characteristics (age, sex, etc.)
- Patient medical history (including family history and bleeding history)
- Social history (level of activity, extracurricular activities)
- Medication list, especially aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], other antiplatelet medications and anticoagulants
- Labs—clotting factors

Assess

- Presence of active bleeding (see "Clinical Manifestations and Diagnosis" section and Table 123-1)
- Presence of common clinical manifestations in bleeding disorders (easy bruising, bleeding after surgery, mucocutaneous bleeding, prolonged menses, etc., and Table 123-1).
- Factor level and the need for prophylactic management

Plan*

- Determine drug therapy regimen (dose, route, frequency, and duration) (see Table 123-3 and "Treatment: Hemophilia" section)
- Monitoring parameters (signs/symptoms of bleeding, frequency of bleeding episodes)
- Patient education/counseling (control of bleeding episodes, administration of drug therapy, when to seek medical attention)
- Continued care at a Hemophilia Treatment Center (or comparable clinic with a comprehensive care team)

Implement

- Provide education and reinforcement of the treatment plan
- Improve adherence through motivational interviewing and open discussions about patient care and the treatment plan
- Schedule regular clinic appointments to assess adherence, bleeding episodes, and to tailor patient therapy

Follow-up: Monitor and Evaluate

- Control and resolution of bleeding signs and symptoms

- Number of bleeding episodes (improvement since beginning care, need for adjustment in the treatment plan)
- Factor level activity (tailor factor doses to patient-specific levels)
- Adherence to the treatment plan (prophylactic and as-needed therapy, seeking medical attention)

**Collaborate with patients, caregivers, and other healthcare professionals.*

BEYOND THE BOOK

BEYOND THE BOOK

Create a Venn diagram to compare hemophilia A and B. Within the diagram, be sure to include pertinent disease state information such as clinical manifestations, incidence, and recommended treatment. List specific short- and long-acting products used in each type, as well as treatment modalities that may be common to both.

INTRODUCTION

The coagulation system is intricately balanced and designed to stop bleeding at the site of vascular injury through complex interactions between the vascular endothelium, platelets, procoagulant proteins, anticoagulant proteins, and fibrinolytic proteins. Hemostasis stops bleeding at the site of vascular injury through the formation of an impermeable platelet and fibrin plug. Three key mechanisms facilitate hemostasis including vascular constriction, primary platelet plug formation (primary hemostasis), and clot propagation through fibrin formation (secondary hemostasis). Derangements in this system can lead to either bleeding or thrombosis. Bleeding disorders are the result of a coagulation factor defect, a quantitative or qualitative platelet defect, or enhanced fibrinolytic activity.

COAGULATION FACTORS

Secondary hemostasis facilitates propagation and stabilization of the initial platelet plug formed in primary hemostasis through the formation of fibrin on the activated platelet surface. This step is initiated via the tissue factor pathway and is vital for adequate hemostasis. Coagulation factors circulate as inactive precursors (zymogens). Activation of these coagulation proteins leads to a cascading series of proteolytic reactions. At each step, a clotting factor undergoes limited proteolysis and becomes an active protease (designated by a lowercase “a,” as in Xa).

The coagulation factors can be divided into three groups based on biochemical properties: vitamin K–dependent factors (II, VII, IX, and X), contact activation factors (XI and XII, prekallikrein, and high-molecular-weight kininogen), and thrombin-sensitive factors (V, VIII, XIII, and fibrinogen). Biologic half-life and blood product source varies by coagulation factor.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The diagnosis of coagulation disorders is established from a detailed clinical history, physical examination, and laboratory test results. The clinical history should ascertain if there is a family history of bleeding or known bleeding disorders. Laboratory testing can distinguish bleeding disorders caused by defects in the coagulation pathways, fibrinolytic pathways, or alterations in the number or function of platelets. Table 123-1 describes common coagulation tests.

TABLE 123-1

Laboratory Procedures

Procedure	Identifies	Possible Cause of Abnormal Value	Clinical Manifestations

Prothrombin time (PT)	Factors I, II, V, VII, X	Newborn Vitamin K deficiency Inherited factor deficiencies[a] Warfarin therapy Liver disease Lupus anticoagulant (rare) Afibrinogenemia Dysfibrinogenemia	Bleeding following surgery, trauma, etc. Easy bruising
Activated partial thromboplastin time (aPTT)	Factors I, II, V, VIII, IX, X	Inherited factor deficiencies[a] Lupus anticoagulant Heparin therapy Liver disease Afibrinogenemia Dysfibrinogenemia	Joint and muscle bleeding Bleeding after surgery, trauma, etc.
	High-molecular-weight kininogen (HMWK), prekallikrein		No bleeding manifestations
	Factor XII		Increased incidence of thrombotic disease possible with severe factor XII deficiency
	Factor XI		Variable bleeding tendency Bleeding following surgery, trauma, etc.
Thrombin time (TT)	Fibrinogen Inhibitors of fibrin aggregation	Afibrinogenemia Dysfibrinogenemia Heparin therapy	Lifelong hemorrhagic disease Variable clinical symptoms from asymptomatic to either a bleeding diathesis or prothrombotic
Platelet count	Thrombocytopenia	Quantitative platelet disorder, type 2B von Willebrand disease, immune thrombocytopenia, other cause of thrombocytopenia	Mucocutaneous bleeding
Platelet function analyzer	Platelet function	Qualitative platelet defects, von Willebrand disease, antiplatelet therapy Also prolonged in anemia and thrombocytopenia[b]	Mucocutaneous bleeding

Platelet aggregation	Gold standard to assess platelet function	Qualitative platelet defects, antiplatelet medications	Mucocutaneous bleeding
Euglobulin clot lysis time (ECLT)	Fibrinolytic defect	A decreased ECLT indicates hyperfibrinolysis, which indicates an abnormality in the fibrinolytic pathway including plasminogen activator inhibitor 1 deficiency, α_2-plasminogen inhibitor deficiency Hypofibrinogenemia	Bleeding after trauma or surgical procedures especially in oral and urogenital areas

[a]Bleeding manifestations depend on factor levels.

[b]Insensitive to mild platelet defects and has fallen out of favor as a screening test

HEMOPHILIA

Hemophilia is a bleeding disorder that results from a congenital deficiency in a plasma coagulation protein. Hemophilia A (classic hemophilia) is caused by a deficiency of factor VIII and hemophilia B (Christmas disease) is caused by a deficiency of factor IX. Hemophilia affects about 400,000 males worldwide.[1] The incidence of hemophilia A is about 1 in 5,000 male births and hemophilia B occurs in 1 in 30,000 male births.[2] Hemophilia A constitutes 80% to 85% of all patients with hemophilia with the other 15% to 20% being hemophilia B.[1] The incidence of hemophilia is not affected by race.

About one-third of patients with hemophilia have a negative family history, presumably representing a spontaneous mutation.[1] Both hemophilia A and hemophilia B are recessive X-linked diseases, which means that the defective gene is located on the X chromosome. The disease primarily affects only males while females are carriers. Since affected males have the abnormal allele on their X chromosome and no matching allele on their Y chromosome, their sons would be normal (assuming the mother is not a carrier) and their daughters would be obligatory carriers. Female carriers have one normal allele and, therefore, do not usually have a bleeding tendency, although female carriers have lower factor VIII levels than females who are not carriers.[3] Sons of a female carrier and a normal male have a 50% chance of having hemophilia and daughters have a 50% chance of being carriers. Thus, there is a “skipped generation” mode of inheritance in which the female carriers do not express the disease but can pass it on to the next male generation. Hemophilia has been observed in a small number of females. It can occur if both factor VIII and IX genes are defective or if a female patient has only one X chromosome as in Turner syndrome.[4]

In 1984, researchers isolated and cloned the human factor VIII gene. It is a large gene, consisting of 186 kilobases (kb).[5] More than 2,000 unique mutations in the factor VIII gene, including point mutations, deletions, and insertions, have been reported.[6] Deletions and nonsense mutations are often associated with the more severe forms of factor VIII deficiency because functional factor VIII is not produced. In 1993, researchers identified an inversion in the factor VIII gene at intron 22 that accounts for almost 30% to 45% of severe hemophilia A gene abnormalities.[1] That discovery has greatly simplified carrier detection and prenatal diagnosis in families with this gene mutation.

The factor IX gene, cloned and sequenced in 1982, consists of only 34 kb and is significantly smaller than the factor VIII gene.[5] Unlike the factor VIII gene in patients with severe hemophilia A, the factor IX gene in patients with hemophilia B has no predominant mutation. Direct gene mutation analysis is simpler in hemophilia B because of the smaller gene size, and to date more than 1,000 different mutations have been reported.[7] Most of these mutations are single base-pair substitutions. About 3% of factor IX gene mutations are deletions or complex rearrangements, and the presence of these mutations is associated with a severe phenotype.[1]

Hemophilia B Leyden is a rare variant in which factor IX levels initially are low but rise at puberty. The mechanism of this disorder is controversial. Some propose that the binding of the androgen receptor and other transcription factors are responsible. Other molecular mechanisms for age-related gene

regulation have been discovered and implicated in factor IX Leyden.[8] Identification of this genotype is clinically important because it confers a better prognosis.

Clinical Presentation and Diagnosis

CLINICAL PRESENTATION: Hemophilia

Signs and Symptoms

- Ecchymoses (palpable/raised)
- Hemarthroses (especially knee, ankle, and elbow)
- Joint pain
- Joint swelling and erythema
- Decreased range of motion
- Muscle hemorrhage
- Swelling at the site of muscle bleeding
- Pain with motion of affected muscle
- Signs of nerve compression
- Significant anemia from an iliopsoas or thigh bleed
- Oral bleeding with dental extractions or trauma
- Hematuria
- Intracranial hemorrhage (spontaneous or following trauma)
- Excessive bleeding with surgery

Laboratory Testing

- Prolonged aPTT
- Decreased factor VIII or factor IX level
- Normal prothrombin time
- Normal platelet count
- Normal von Willebrand factor antigen and activity
- Normal bleeding time

The characteristic bleeding manifestations of hemophilia include palpable ecchymosis, bleeding into joint spaces (hemarthroses), muscle hemorrhages, and excessive bleeding after surgery or trauma. The severity of clinical bleeding generally correlates with the degree of deficiency of either factor VIII or factor IX. Factor VIII and factor IX activity levels are measured in units per milliliter, with 1 unit/mL representing 100% of the factor found in 1 mL of normal plasma.[2] Normal plasma levels range from 0.5 to 1.5 units/mL (50%-150%). Patients with less than 0.01 units/mL (1%) of either

factor are classified as having severe hemophilia, those with between 0.01 and 0.05 units/mL (1%-5%) are moderate, and those with between 0.05 and 0.4 units/mL (5%-40%) have mild hemophilia.

Patients with severe disease experience frequent spontaneous hemorrhages, while those with moderate disease have excessive bleeding following mild trauma and rarely experience spontaneous hemarthroses. Patients with mild hemophilia may have few symptoms that their condition can be undetected for many years and they usually have excessive bleeding only after significant trauma or surgery. Disease severity does not always correlate with disease manifestations. Those with severe disease (<1% [0.01 units/mL] factor activity) may occasionally not display a severe phenotype, while some with milder forms of the disease may have more severe bleeding. Prolonged bleeding after circumcision is a common presenting sign. Most patients will have some manifestation of the disease sometime after their first year of life when they begin to walk and increase their risk of bleeding due to falling.[1]

The diagnosis of hemophilia should be considered in any male with unusual bleeding. A family history of bleeding is helpful in the diagnosis but is absent in up to 50% of patients with about one-third representing spontaneous mutations and the remaining secondary to unrecognized family history.[5] Brothers of patients with hemophilia should be screened; sisters should consider undergoing carrier testing. Laboratory testing in patients with hemophilia will usually reveal an isolated prolonged partial thromboplastin time and they will have a decreased factor VIII or factor IX level.

Patients with severe hemophilia A should be tested for the common factor VIII gene inversions. In patients with severe hemophilia A who lack an inversion mutation or in patients with moderate or mild hemophilia A, the gene can be sequenced to determine the exact mutation if needed. The exact mutation can determine carrier status but is not done routinely because it is very costly and does not change therapy. Techniques to determine the genetic mutation in patients with hemophilia B are similar, but no predominant mutation like the factor VIII inversion has been found. The smaller size of the factor IX gene facilitates direct DNA mutational analysis.[7]

Hemophilia can be diagnosed prenatally, if desired, by chorionic villus sampling in gestational weeks 9 to 14 or by amniocentesis after 15 to 17 weeks of gestation.[1,9] These are invasive procedures with a 0.5% to 1% chance for pregnancy loss so it is not routinely done.[9] A new noninvasive method uses cell-free fetal DNA in maternal circulation to determine the sex of the fetus; more invasive testing is required for a male fetus.[9] This method was used to successfully identify hemophilia mutations but is still experimental and requires further validation.[10]

Treatment: Hemophilia

2 The comprehensive care of hemophilia requires an interprofessional team approach. The patient is best managed in specialized centers with trained personnel and appropriate laboratory, radiologic, and pharmaceutical services.[1] The healthcare team should include hematologists, orthopedic surgeons, nurses, physical therapists, dentists, genetic counselors, psychologists, pharmacists, case managers, and social workers who have experience in caring for patients with bleeding disorders. The goal for comprehensive hemophilia care is to prevent bleeding episodes and their long-term sequelae so that patients with hemophilia can live full, active, and productive lives.

Patients with hemophilia should receive routine immunizations, including immunization against hepatitis B. Hepatitis A vaccine is also recommended for patients with hemophilia because of the risk (albeit small) of transmitting the causative agent through factor concentrates. The administration of vaccines is preferred subcutaneously in patients with severe disease.[1,11] If intramuscular administration is required, the use of a small-gauge needle with cold compresses and pressure to the site can prevent excessive bleeding.

A few special considerations apply to the perinatal care of male infants of hemophilia carriers. Intracranial or extracranial hemorrhage occurs in 1% to 2% of newborns with hemophilia.[7] Vacuum extraction and forceps delivery increase the risk of cranial bleeding. Elective cesarean section does not prevent intracranial bleeding. The optimal mode of delivery or the use of prophylactic factor replacement in male infants of hemophilia carriers is controversial.[1] Circumcision should be postponed until a diagnosis of hemophilia is excluded. Factor levels can be assayed from cord blood samples or from peripheral venipuncture. Arterial puncture should be avoided because of the risk of hematoma formation. If an infant has hemophilia, many clinicians recommend a screening head ultrasound to rule out an intracranial hemorrhage prior to discharge from the nursery.[1,12]

Prophylaxis

The prevention of bleeding episodes and their resulting long-term complications is the mainstay of treatment for hemophilia. This can be

accomplished through the regular administration of factor products or non-factor products to maintain hemostasis and prevent bleeding. It should begin early in life (before the age of 3 years old) to prevent musculoskeletal complications associated with joint or muscle bleeds. The goal of prophylaxis is to maintain a minimum factor activity or hemostasis level which would allow the patient to live a healthy and active life. Prophylaxis for patients with severe hemophilia is considered to be the standard of care recommended by the World Health Organization and the World Federation of Hemophilia (WFH).[1] Prophylaxis is sometimes required in patients with moderate hemophilia but is rarely used in patients with mild hemophilia.

Age at initiation of prophylaxis is a strong predictor of long-term clinical outcomes. Primary prophylaxis is started at a young age (usually before age 2 years), prior to the onset of joint bleeding.[13] Secondary prophylaxis begins after significant joint bleeding has already occurred.[13] In 2001, the Medical and Scientific Advisory Council of the National Hemophilia Foundation of the United States recommended primary prophylaxis beginning at age 1 to 2 years for children with severe hemophilia.

Prophylaxis with Factor Replacement

Prophylactic factor replacement therapy is the regular intravenous administration of the deficient factor to maintain adequate activity levels to prevent bleeding. This effectively converts severe hemophilia into a milder form of the disease. The rationale for this approach is that patients with moderate hemophilia rarely experience spontaneous hemarthroses, and they have a much lower risk of chronic arthropathy. Many clinical trials proved the efficacy of a prophylactic approach in pediatric patients both in previously treated and untreated patients. The common finding is that prophylaxis prevented joint damage and decreased the frequency of joint and other hemorrhages.[13,14]

The dosing for prophylactic regimens varies considerably and no one regimen has been proven to be superior. Early on, patients with hemophilia A would be dosed on an every other day or three times a week regimen of standard half-life (SHL) factor VIII. For hemophilia B, the usual dosing of standard half-life factor IX would be twice weekly because of the intrinsically longer half-life.[1] The recent introduction of extended half-life factor products has made prophylaxis a more feasible approach (see Table 123-2). Patients with hemophilia A can now be dosed with an extended half-life product at 3- to 5-day intervals depending on their individual response.[14,15] Similarly, patients with hemophilia B can be dosed with an extended half-life product once weekly or every 10 to 14 days.[15] The extended half-life factor products allow for a much more ambitious dosing approach achieving higher activity levels in the mild and non-hemophilic range for substantial periods of time.[1]

Prophylactic factor replacement therapy comes with its own set of challenges. In addition to the paucity of standardized regimens, a significant challenge is the high cost of this approach. The cost to treat a patient with hemophilia A in the United States is about $300,000 per year.[16] Other issues to consider are the inconvenience to families and possible difficulties with adherence. Central venous lines may be necessary for frequent administration of factor concentrates, particularly in children younger than 2 years, who are at the age when primary prophylaxis is considered. Potential complications of central venous access include surgical risks, infection, and catheter-related deep-vein thrombosis.[1]

Prophylaxis with Nonfactor Products

While prophylaxis with factor products has been the mainstay of hemophilia treatment, the landscape is changing with the development of new therapeutic approaches and products for hemostasis. Non-factor replacement products for prophylaxis differ from the factor products in that they obtain hemostasis through unique mechanisms. This is an area of growing research. The only commercially available product for this purpose is emicizumab for hemophilia A. Emicizumab is a recombinant, humanized, bispecific monoclonal antibody that bridges activated factor IX and factor X, performing the function of the missing activated factor VIII in maintaining hemostasis in patients with hemophilia A. Due to its unique structure, the risk of developing neutralizing antibodies to the drug is low and it is not affected by the patient's preexisting inhibitors (neutralizing antibodies) to factor VIII if present. Due to a prolonged half-life of 4 weeks, it can be administered in a single subcutaneous injection once weekly and in some cases every 2 to 4 weeks. The safety and efficacy of emicizumab has been demonstrated in children and adults with hemophilia A for prophylaxis therapy in the HAVEN 1-4 trials.[17,18]

In patients with inhibitors, emicizumab is much more effective than previously utilized prophylaxis modalities such as recombinant activated factor VII or activated prothrombin complex concentrates (aPCC). In non-inhibitor patients, emicizumab reduces the annual bleeding rate, or ABR even lower than some reported trials in patients receiving factor replacement prophylaxis. The subcutaneous administration of emicizumab is allowing prophylaxis to start even earlier in children 6 to 12 months of age without the need for indwelling central lines. It avoids the peaks and troughs associated with prophylactic factor replacement therapy and is much more convenient for patients and families potentially increasing adherence and

thereby improved outcomes.[1]

With the success of emicizumab and the promise of future non-factor products on the way, the concepts and definitions of prophylaxis for hemophilia patients are shifting to be more inclusive of a wide variety of mechanisms of action and modalities of administration. The WFH is proposing a new definition based on outcomes rather than doses of products used or age of initiation. They propose the following as a modern definition of prophylaxis: the regular administration of a hemostatic agent/agents with the goal of preventing bleeding in people with hemophilia while allowing them to lead active lives and to achieve a quality of life comparable to a non-hemophilic individual.[1]

Hemophilia A

Therapy for hemophilia has undergone dramatic advances over the past few decades. Fifty years ago, the administration of fresh-frozen plasma was the only available treatment. The introduction of cryoprecipitate in the early 1960s allowed more specific therapy for hemophilia A.[19] Intermediate-purity factor VIII and IX plasma-derived concentrates became available in the 1970s.[19] Plasma-derived factor concentrates are made from the donations of thousands of people. Contamination of plasma pools with hepatitis B, hepatitis C, and the human immunodeficiency virus (HIV) during the late 1970s and early 1980s resulted in transmission to a large portion of patients with hemophilia. Since the mid-1980s, plasma-derived concentrates have been manufactured with a variety of virus-inactivating techniques, including dry heat, pasteurization, and treatment with chemicals (eg, solvent detergent mixtures).[5] Since 1986, no transmission of HIV through factor concentrates to patients with hemophilia in the United States has been reported.[5] Protein purification techniques, introduced in the 1990s, led to the production of high-purity plasma-derived concentrates with increased amounts of factor VIII or factor IX relative to the product's total protein content. Recombinant factor VIII and then factor IX also became available in the 1990s.[19] Significant improvements have been made with recombinant products in limiting the risk of infectious transmission from albumin used to stabilize some of the products. Like plasma-derived products, these products use viral inactivation steps. With each subsequent generation of recombinant factor VIII products, the use of human proteins has been reduced.[19]

Significant advancements have taken place in the development of long-acting factor VIII and IX products some of which are Food and Drug Administration approved and commercially available. Methods for prolonging the half-life of these products include pegylation and Fc fusion.[20] Pegylation is thought to increase half-life by protecting the factor from receptor-mediated uptake and enzymatic catabolism. It reduces renal clearance and levels of neutralizing antibodies due to steric hindrance.[19] Protein fusion has also been a successful approach to prolonging the half-life of factor products. This method fuses factor VIII or IX to another human protein with a long circulatory half-life such as albumin or immunoglobulin G (IgG). These fused proteins then bind to the neonatal Fc receptor, or FcRn, present in the acidified endosomes of the endothelial cells. This binding protects the factor fusion product from targeted lysosomal degradation and facilitates recycling of the neonatal Fc receptor ligands at the endothelial surface resulting in a prolonged systemic half-life of the factor.[21,22]

Table 123-2 summarizes many of the factor VIII products available in the United States. Most patients are treated with high-purity products, which generally have the lowest risk of transmitting infectious disease and are therefore recommended as first-line agents.[1] Recombinant products, when available, are generally used rather than plasma-derived products.

TABLE 123-2

Factor Concentrates

Plasma Derived	Recombinant	Extended Half-Life

• **Factor VIII**
  ○ Hemofil M
  ○ Koate DVI
  ○ Monoclate P
• **Factor VIII + vWF**
  ○ Alphanate
  ○ Humate P
  ○ Wilate
• **Factor IX**
  ○ AlphaNine
  ○ Mononine
• **PCC**
  ○ Bebulin
  ○ Kcentra
  ○ Profilnine
• **aPCC**
  ○ FEIBA
	• **Factor VIII**
	  ○ Advate
	  ○ Afstyla
	  ○ Helixate
	  ○ Kogenate
	  ○ Kovaltry
	  ○ Obizur (PS)
	  ○ Recombinate
	  ○ Nuwiq
	  ○ NovoEight (BDD)
	  ○ Xyntha (BDD)
	• **Factor IX**
	  ○ BeneFIX
	  ○ Ixinity
	  ○ Rixubis
	• **Factor VII**
	  ○ NovoSeven
	• **vWF**
	  ○ Vonvendi
		• **Factor VIII**
		  ○ Adynovate (PEG)
		  ○ Jivi (PEG)
		  ○ Eloctate (Fc-IgG)
		• **Factor IX**
		  ○ Alprolix (Fc-IgG)
		  ○ Idelvion (FP)
		  ○ Rebinyn (PEG)

BDD, B-domain deleted; Fc-IgG, fusion protein IgG; FP, fusion protein–albumin; PCC, prothrombin complex concentrate; PEG, pegylated; PS, porcine sequenced; vWF, von Willebrand Factor.

Recombinant Factor VIII

Recombinant factor VIII is produced with recombinant DNA technology and is derived from cultured Chinese hamster ovary cells or baby hamster kidney cells transfected with the human factor VIII gene.[5] Since these products are not derived from blood donations, the risk of transmitting infections through administration of recombinant factor VIII is low and recombinant products are generally favored over plasma-derived products. A small risk of viral infection of the cell lines used to produce the clotting factor still remains. Furthermore, human or animal proteins are used in the production process of some recombinant products.[19] Therefore, these products have a theoretical risk of transmitting infection, although hepatitis and HIV infection have never been reported with their use.[5] First-generation recombinant factor VIII products contain human albumin as a stabilizing protein.[5] Second-generation recombinant factor VIII products add sugar instead of human albumin as a stabilizer, but human albumin is used in the culture process. Several products are manufactured specifically with the B domain of the factor VIII gene deleted, yielding a smaller protein product.[5,23] This B domain does not appear to be necessary for coagulation function and may serve as a binding site for neutralizing antibodies. Third-generation recombinant factor VIII products do not contain human protein either in the culture or in the stabilization processes.[19]

Plasma-Derived Factor VIII Products

The recombinant factor VIII products are comparable in effectiveness to plasma-derived products.[5] Several different plasma-derived factor VIII products are available (Table 123-2). These products are derived from the pooled plasma of thousands of donors and therefore have the potential to transmit infection. Donor screening, testing of plasma pools for evidence of infection, viral reduction through purification steps, and viral inactivation

procedures (eg, dry heat, pasteurization, and solvent detergent treatment) have resulted in a safer product. No cases of HIV transmission from factor concentrates have been reported since 1986.[5] However, isolated cases of hepatitis C infection with the use of plasma-derived products have been reported.[5] Additionally, outbreaks of hepatitis A viral infections associated with plasma-derived products have been reported, likely because solvent detergent treatment does not inactivate this nonenveloped virus. Finally, possible infection with unidentified viruses not inactivated by the currently used methods remains a concern. In addition, Prion disease may be present in plasma-derived factor products.[24]

Factor VIII concentrates can be classified according to their level of purity, which refers to the specific activity of factor VIII in the product. Cryoprecipitate is a low-purity product that also contains vWF, fibrinogen, and factor XIII. The American Association of Blood Banks standards call for a minimum of 80 international units of factor VIII per cryoprecipitate pack.[5] This product is no longer considered a primary treatment of factor VIII deficiency in countries where factor VIII concentrates are available because cryoprecipitate does not undergo a viral inactivation process. Intermediate-purity products have a specific factor VIII activity of 5 units/mg of protein and high-purity products have up to 2,000 units/mg of protein.[5] Ultrahigh-purity plasma-derived products are prepared with monoclonal antibody purification steps and have a specific activity of 3,000 units/mg of protein prior to addition of albumin as a stabilizer.

Factor VIII: Dosing

Appropriate dosing of factor VIII concentrate depends on the half-life of the infused factor, the patient's body weight, and the location and severity of the bleed. The presence or absence of an inhibitory antibody to factor VIII and the titer of this antibody also influence treatment. Recovery studies, which measure the immediate postinfusion factor level, and survival studies, which assess the half-life of the factor, can establish patient-specific pharmacokinetics. The location and magnitude of the bleeding episode determine the percent correction to target as well as the duration of treatment. Serious or life-threatening bleeding requires peak factor levels of greater than 0.75 to 1 units/mL (75%-100%); less severe bleeding may be treated with a goal of 0.3 to 0.5 units/mL (30%-50%) peak plasma levels. Table 123-3 provides general guidelines for the management of bleeding in different locations.

TABLE 123-3

Guidelines for Factor Replacement Therapy for Hemorrhage in Hemophilia A and B

Site of Hemorrhage	Desired Hemostatic Factor Level (% of Normal)	Comments
Joint	50%-70%, 2-3 days	Rest/immobilization/physical therapy rehabilitation following bleed; several doses may be necessary to prevent or treat target joint
Muscle	30%-50% for most sites	Risk of significant blood loss with a thigh or iliopsoas bleed; bed rest for iliopsoas or thigh bleeding
	70%-100% for thigh, iliopsoas, or nerve compression	
Oral mucosa	30%-50%	May try antifibrinolytic or topical thrombin prior to factor replacement for minor bleeding; higher factor levels are needed for tongue swelling or risk of airway compromise; antifibrinolytic therapy should be used following factor replacement
Gastrointestinal	Initially 100%, then 40%-60%	Endoscopy is highly recommended; antifibrinolytic therapy may be useful; continue until healing occurs
Hematuria	30%-50% if no trauma	If no pain or trauma, consider bed rest and fluids for 24 hours; factor should be given if hematuria persists; evaluate if hematuria persists; if trauma to abdomen or back, perform imaging and give aggressive factor replacement
	70%-100% if traumatic	
Central nervous system	Initially 100%, then 50%-100% for 10-21 days	Lumbar puncture requires prophylactic factor coverage
Trauma or surgery	Initially 100%, then 50%-100% until wound healing complete	The perioperative and postoperative management plan must be in place preoperatively; evaluation for inhibitors is crucial prior to elective surgery

Factor VIII is a large molecule that remains in the intravascular space. Therefore, the plasma volume (about 50 mL/kg) can be used to estimate the volume of distribution. In general, each unit of factor VIII concentrate infused per kilogram of actual body weight results in a 2% rise in plasma factor VIII levels.[1] The following equation can be used to calculate an initial dose of factor VIII:

$$\text{Factor VIII (units)} = (\text{Desired level} - \text{Baseline level}) \times 0.5 \times (\text{Weight [in kilograms]})$$ Factor VIII (units)=(Desired level - Baseline level)× 0.5×(Weight [in kilograms])

The baseline level usually is omitted from the equation when it is negligible compared to the desired level. The half-life of factor VIII ranges from 8 to 15 hours. It is generally necessary to administer 50% of the initial dose about every 12 hours to sustain the desired level of factor VIII. A single treatment may be adequate for minor bleeding, such as oral bleeding or slight muscle hemorrhages. However, because of the potential for long-term joint damage with hemarthroses, 2 or 3 days of treatment is often recommended for these bleeds. Serious bleeding episodes may require maintenance of 70% to 100% (0.7-1.0 units/mL) factor activity for 1 week or longer. As previously mentioned, factor VIII dosing depends on several variables, and each case must be considered individually. Individualized pharmacokinetics may help guide treatment, particularly for serious bleeding episodes.

Alternatively, factor VIII can be administered as a continuous infusion when prolonged treatment is required (eg, in the perioperative period or for serious bleeding episodes). Infusion rates ranging from 2 to 4 units/kg/hr usually are given in fixed-dose continuous infusion protocols, with the aim of maintaining a steady-state level of 60% to 100% (0.6-1.0 units/mL).[25] Administration of factor concentrate via continuous infusion may reduce factor

requirements by 20% to 50% because unnecessarily high peaks of factor VIII that occur with bolus injections are avoided. A gradual decrease in factor VIII clearance during the first 5 to 6 days of treatment contributes to the lower factor concentrate requirements. Daily monitoring of factor level can help determine the appropriate rate of infusion.

Administration of factor VIII concentrate via continuous infusion is safe and effective, and it may be more convenient than bolus therapy for hospitalized patients.[26] Concerns about the stability of the formulations appear to be unwarranted, as most high-purity factor VIII concentrates remain stable for at least 7 days after reconstitution.[26] However, exposure of factor VIII to light for 10 hours after reconstitution can decrease activity by 30% (0.3 units/mL).[26] Therefore, it would be prudent to shield the container with foil wrap or an appropriate bag.

Other Pharmacological Therapy

Treatment with desmopressin acetate often is adequate for minor bleeding episodes in patients with mild hemophilia A. A synthetic analog of the antidiuretic hormone vasopressin, desmopressin causes the release of vWF and factor VIII from endogenous endothelial storage sites. It is most effective in patients with higher baseline factor VIII levels (0.1-0.15 units/mL [10%-15%]).[25] The recommended dose of desmopressin is 0.3 mcg/kg diluted in 50 mL of normal saline and infused IV over 15 to 30 minutes.[25] Patients with mild or moderate hemophilia A should undergo a desmopressin trial to determine their response to this medication. At least a twofold rise in factor VIII to a minimal level of 0.3 units/mL (30%) within 60 minutes is considered an adequate response.[1,25] Infusion of desmopressin can be repeated daily for up to 2 to 3 days. Tachyphylaxis, an attenuated response with repeated dosing, may develop after that time due to the depletion of factor stores. The factor increase after the second dose of desmopressin is about 30% lower than after the initial dose.[27] Factor concentrate therapy may be necessary if the patient requires additional treatment. Factor levels should be monitored to ensure that an adequate response has been achieved. Treatment with desmopressin will not result in hemostasis in patients who have severe hemophilia and those who are only marginally responsive. Desmopressin should not be used as primary therapy for life-threatening bleeding episodes such as intracranial hemorrhage or for major surgical procedures.[1]

Desmopressin can be administered intranasally via a concentrated nasal spray.[25] It elicits a slower and less marked response, with a peak effect in 60 to 90 minutes after administration, which is somewhat longer than with IV administration.[25,27] The dosage is one spray (150 mcg) in one nostril for patients who weigh less than 50 kg and two sprays (one in each nostril, 300 mcg total) for those who weigh more than 50 kg.[25] The nasal spray may serve as an alternative to the IV formulation, especially in patients with mild bleeding episodes. Few adverse drug reactions are associated with desmopressin. The most commonly observed adverse drug reaction is facial flushing.[27] Less frequently reported adverse drug reactions include mild headaches, increased heart rate, and decreased blood pressure. Desmopressin can cause water retention because of its antidiuretic effects, which may lead to severe hyponatremia. This may be a particular problem in children younger than 2 years and, therefore, should be used with caution in this age group.[25] Fluid restriction for 24 hours after the desmopressin dose and monitoring of urine output are recommended with desmopressin administration.[25]

Antifibrinolytic therapy inhibits clot lysis and therefore is a useful adjunctive therapy for the treatment of hemophilia, primarily with mucocutaneous bleeding. Antifibrinolytic agents are particularly beneficial for the treatment of oral bleeding because of a high concentration of fibrinolytic enzymes in saliva. Antifibrinolytic therapy can also be helpful as adjuvant therapy in GI bleeding, epistaxis, and menorrhagia. Antifibrinolytic therapy should be used with caution in patients with urinary bleeding, due to the risk of obstruction and subsequent renal toxicity. The two available antifibrinolytics include aminocaproic acid and tranexamic acid. Aminocaproic acid is given at a dosage of 100 mg/kg (maximum 6 g) every 6 hours and can be administered orally or IV.[5] The dosage of tranexamic acid is 25 mg/kg (maximum 1.5 g) orally every 6 to 8 hours.[5]

Hemophilia B

Therapeutic options for hemophilia B have improved greatly over the past several years, first with the development of monoclonal antibody-purified plasma-derived products and then with the licensure of recombinant factor IX. Products available in the United States for treatment of hemophilia B are listed in Table 123-2.

Recombinant Factor IX

Recombinant factor IX was not available until 1998, which is 6 years after the first recombinant factor VIII product.[19] The first commercially available

recombinant factor IX is produced in Chinese hamster ovary cells transfected with the factor IX gene. Since blood and plasma products are not used to produce recombinant factor IX or to stabilize the final product, recombinant factor IX has an excellent viral safety profile.[5] Clinical trials have proved the safety and efficacy of the product in the treatment of acute bleeding episodes and in the management of bleeding associated with surgical procedures.[5] Although the half-life of recombinant factor IX is similar to that of the plasma-derived products, recovery is about 30% lower.[25] As a result, doses of recombinant factor IX concentrate must be higher than those of plasma-derived products to achieve equivalent plasma levels. Because individual pharmacokinetics may vary, recovery and survival studies should be performed to determine optimal treatment.[5] Recombinant factor IX is considered the treatment of choice for hemophilia B.[1]

Plasma-Derived Factor IX Products

High-purity factor IX plasma concentrates have been available in the United States since the early 1990s.[5,19] These products are derived from plasma through biochemical purification and monoclonal immunoaffinity techniques. Other viral inactivation measures, such as solvent detergent or chemical treatment, are also used. High-purity factor IX concentrates have excellent efficacy in the treatment of bleeding episodes and in the control of bleeding associated with surgical procedures.[25] Their viral safety profile has been reported to be excellent and the risk of thromboembolic complications is low.

Before the high-purity products were approved for use, hemophilia B patients were treated with factor IX concentrates that also contained other vitamin K–dependent proteins (factors II, VII, and X), known as prothrombin complex concentrates (PCCs). These products contain small amounts of activated factors generated during processing, and their use has been associated with thrombotic complications, including deep-vein thrombosis, pulmonary embolism, myocardial infarction, and disseminated intravascular coagulation.[5,25] The risk of these complications is highest in patients receiving high or repeated doses of PCCs, in those with hepatic disease (the liver produces antithrombotic factors and removes the activated factors from circulation), in neonates, and in patients who have experienced crush injuries or who are undergoing major surgery.[5] Concomitant use of PCCs and antifibrinolytics should be avoided because of the risk for thrombosis. Because of the lower purity of PCCs and their thrombogenic potential, these products are not first-line treatment for hemophilia B.

Factor IX: Dosing

Factor IX is a relatively small protein. Unlike factor VIII, it is not limited to the intravascular space; it also passes into the extravascular compartment.[5] Therefore, it has a volume of distribution that is about twice that of factor VIII. For plasma-derived factor IX concentrates, each unit of factor IX infused per kilogram of actual body weight results in about a 1% (0.01 units/mL) rise in the plasma level of factor IX (range, 0.67%-1.28% [0.0067-0.0128 units/mL]).[5] The following equation can be used to calculate the initial dose:

$$\text{Plasma} - \text{derived factor IX (units)} = (\text{Desired level} - \text{Baseline level}) \times (\text{Weight [in kilograms]})$$Plasma-derived factor IX (units) = (Desired level - Baseline level) × (Weight [in kilograms])

As with the factor VIII dose calculation, the baseline level term can be omitted from the formula if it is negligible compared to the desired level. Because recovery of recombinant factor IX is lower than that of the plasma-derived products, the following adjustment is made:

Pediatric dosing:

$$\text{Recombinant factor IX (units)} = (\text{Desired level} - \text{Baseline level}) \times 1.4 \times (\text{Weight [in kilograms]})$$Recombinant factor IX (units) = (Desired level - Baseline level) × 1.4 × (Weight [in kilograms])

Adult dosing:

$$\text{Recombinant factor IX (units)} = (\text{Desired level} - \text{Baseline level}) \times 1.2 \times (\text{Weight [in kilograms]})$$Recombinant factor IX (units) = (Desired level - Baseline level) × 1.2 × (Weight [in kilograms])

A recovery study to determine optimal dosing is recommended for patients who receive recombinant factor IX because of the wide interpatient variability in pharmacokinetics. Because the half-life of factor IX is about 24 hours, dosing can be less frequent than with factor VIII. Table 123-3 provides general guidelines for dosing factor IX based on the site and severity of the bleeding episode.[25]

Treatment of Inhibitors

Neutralizing antibodies to factors VIII and IX, known as *inhibitors*, develop in a subset of patients with hemophilia. The development of an inhibitor is the most serious complication of factor replacement therapy and is associated with considerable morbidity and a decreased quality of life. The incidence of new factor VIII inhibitors in patients with severe factor VIII deficiency is about 30%.[28] Inhibitors are less common in patients with mild or

moderate hemophilia occurring in about 5% to 10% of patients.[1] The risk of developing inhibitors in patients with hemophilia B is much lower, occurring in only 3% of patients.[5]

An inhibitor is a polyclonal high-affinity IgG directed against the factor VIII or IX protein. Inhibitors interfere with infused factor concentrate, rendering them ineffective. The presence of an inhibitor is suspected when a decreased clinical response to factor replacement is observed or it may be discovered incidentally on routine laboratory screening. Inhibitors are measured with the Bethesda assay, and titers are reported in Bethesda units (BUs). One BU is the amount of inhibitor needed to inactivate half of the factor VIII or factor IX in a mixture of inhibitor-containing plasma and pooled normal plasma.[5] Patients with inhibitors to factor VIII or factor IX are divided into two groups: low responders, who have low levels of inhibitors (5 BU/mL), and high responders who have higher inhibitor levels (>5 BU/mL) and develop an increase in antibody titer after exposure (anamnestic response).[5,29]

Most inhibitors develop in childhood, after relatively few exposure days (median 9-12 days).[30] Patients with severe hemophilia are much more likely to develop inhibitors than those with milder forms of the disease.[29] It is possible that the low levels of factor produced in patients with mild or moderate hemophilia induce immune tolerance in these individuals. In contrast, factor levels are undetectable in patients with severe hemophilia, so infused factor VIII is regarded as a foreign protein, which may provoke an antibody response. The rate of inhibitor formation varies even among patients with identical mutations, which suggests that host factors modify the risk. The development of an inhibitor is the result of a complex interaction between a patient's immune system and genetic and environmental risk factors.

The type of factor product administered to patients may influence the risk of developing inhibitors. An international, multicenter, randomized, open-label clinical trial named Survey of Inhibitors in Plasma-Product Exposed Toddlers, or SIPPET, was designed to evaluate the incidence of inhibitor development in previously untreated or minimally treated patients with hemophilia A exposed to plasma-derived factor products compared to recombinant products.[31] The results of this pivotal trial showed that patients receiving recombinant factor VIII products had a significantly higher incidence of developing inhibitors compared to those receiving plasma-derived products.

Therapy for patients with inhibitors involves the treatment of acute bleeding episodes and treatment directed at eradicating the inhibitor. The inhibitor titer, the site and magnitude of bleeding, and the patient's past response to bypassing therapy determine the approach to the treatment of acute bleeding. For patients with a low inhibitor titer, the administration of high doses of the specific factor often can control bleeding episodes. Two to three times the usual replacement dose and more frequent dosing intervals are often necessary to overcome the antibody. Factor-level monitoring and clinical assessments help to evaluate the adequacy of treatment. Additional supportive measures, such as immobilization and administration of antifibrinolytic agents, should be used, where appropriate.[1]

Treatment of acute bleeds in patients with high-titer inhibitors can be complicated and require the use of alternative agents. In the presence of a high-titer inhibitor, it is impossible to administer enough factor VIII or factor IX to neutralize the antibody and achieve a hemostatic plasma level. Therefore, the treatment of bleeding episodes consists of agents that bypass the factor to which the antibody is directed. These bypassing agents include PCCs, aPCCs, and recombinant factor VIIa. PCCs contain the vitamin K–dependent factors II, VII, IX, and X. Small quantities of activated factors are present in these products. Activated PCCs contain greater quantities of the activated factors, primarily factor X and prothrombin. The only available aPCC product in the United States is FEIBA® (Factor Eight Inhibitor Bypassing Agent). The recommended dosage is 50 to 100 units/kg administered every 8 to 12 hours, depending on the severity of the bleeding episode and the maximum dose should not exceed 200 units/kg/day.[15] Activated PCCs appear to be more effective than PCCs and are preferred in patients with inhibitors. As previously mentioned, serious thrombotic complications, including pulmonary emboli, deep-vein thrombosis, and myocardial infarction, have been associated with the use of PCCs and aPCCs.[15] Other minor adverse drug reactions include dizziness, nausea, hives, flushing, and headaches. Patients with factor IX inhibitors occasionally develop severe allergic reactions in response to infusion of factor IX-containing products, so these patients should be monitored closely.[29]

5 Recombinant factor VIIa is effective for the treatment of acute bleeds in patients with hemophilia A or B who have developed inhibitors. Recombinant factor VIIa is a bypassing agent that is thought to be hemostatically active only at the site of tissue injury where the tissue factor is present. Recombinant factor VIIa is not a plasma-derived product, so both viral transmission and anamnestic responses to factor VIII or factor IX are unlikely. The initial recommended dose for bleeding episodes is 90 mcg/kg.[15] However, depending on a patient's response, higher doses up to 300 mcg/kg can be used. A drawback is the product's short half-life, which necessitates initial dosing every 2 hours. Continuous infusion of recombinant factor VIIa, which may be more convenient and cost-effective, has been reported.[32] Patients treated with bypassing agents must be monitored clinically

because no laboratory test directly measures the effectiveness of treatment.

Both recombinant factor VIIa and aPCCs are effective in the treatment of bleeding for patients with inhibitors. In determining which bypassing product to use in an individual patient, the clinician must consider multiple factors. In a patient with a newly diagnosed inhibitor, it is prudent to use recombinant factor VIIa because aPCCs contain a small amount of factor VIII or IX and increase the inhibitor titer. It is also important to consider an individual's response to specific bypassing agents because of the significant variability in response between individuals. In some patients, bleeding can be unresponsive to monotherapy and may require alternating products.[33] Due to the risk of developing thrombosis or disseminated intravascular coagulation from alternating bypassing agents, this therapy should be used with caution and only in an inpatient setting.[15]

In the past, plasma-derived porcine factor VIII was an alternative therapeutic option for patients who have hemophilia A and inhibitors. It was removed from the market secondary to contamination with porcine parvovirus. The rationale for its use is that porcine factor VIII is enough like human factor VIII to participate in the coagulation cascade, yet most factor VIII inhibitors have absent or only weak neutralizing activity against nonhuman factor VIII making this an effective agent to treat an acute bleed. Unfortunately, cross-reactivity with porcine factor VIII does occur, and a high titer of antibody against porcine factor VIII can develop and hypersensitivity to porcine proteins can occur. A recombinant porcine factor VIII has been approved, but only for the treatment of acute bleeds in patients with acquired hemophilia A.[15,34]

The hemostatic therapies for patients with an inhibitor have limited effectiveness leading to significant morbidity and a decreased quality of life. The ideal therapy for patients with an inhibitor is total eradication so that optimal hemostatic treatment with either factor VIII or IX is possible. At this time, the only proven method for inhibitor eradication is immune tolerance induction (ITI), which involves the regular infusion of factor VIII to induce antigen-specific tolerance. This approach is not recommended for patients with hemophilia B who have developed inhibitors due to the risk of hypersensitivity reactions and anaphylaxis associated with factor IX administration in this group.

Multiple immune tolerance registries were established to help determine patient- and treatment-related factors associated with immune tolerance outcome.[35] Across these registries, a patient's peak historical factor VIII inhibitor titer (<200 BU) and the inhibitor titer at the time of ITI induction (<10 BU) were associated with successful immune tolerance. The overall ITI success rate from these registries ranges from 51% to 79%; the variability is likely related to a lack of standardization in study methodologies, treatment protocols, and eradication definitions.[35,36]

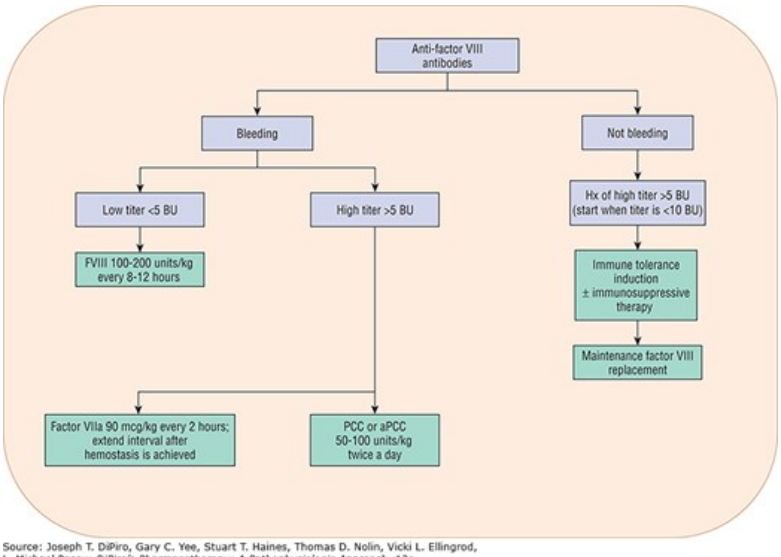
The relationship between factor VIII dose and ITI success rate is not clear. A variety of different dosing regimens, ranging from 25 units/kg every other day to more than 200 units/kg every day, have been used. The International Immune Tolerance Registry demonstrated improved ITI success with high doses (200 IU/kg), while the North American and Spanish Immune Tolerance Registries showed improved success with lower dosing strategies.[36] The International Immune Tolerance Study is a multicenter randomized clinical trial that compared high-dose (200 units/kg/day) to low-dose (50 units/kg three times/week) regimens in patients with severe hemophilia A and high titer inhibitors (>5 BU).[35] This study was stopped early due to an increased risk of bleeding events in the low-dose arm. At the stopping point, the proportion of ITI success was not significantly different between the two arms, but the time to achieve ITI success was shorter in the high-dose arm. Because the study was stopped early, it lacked statistical power to demonstrate therapeutic equivalence below the 30% boundary of equivalence. A high-dose strategy achieves tolerance at a faster rate, which explains the lower bleeding rate.

Some studies report better success rates for ITI in patients receiving plasma-derived factor products containing vWF, which may be related to the role of vWF in factor VIII function, stabilization, and immunogenicity.[37] vWF binding to the C2 domain of factor VIII, a common site for inhibitor formation, may result in epitope masking and decreased inhibitor activity. The use of vWF-containing products may also extend the plasma half-life of factor VIII during ITI; thus, increasing antigen presentation and possibly contributing to its overall success.[37]

Although not commonly used in ITI protocols, immune modulation can improve tolerance success. Agents such as cyclophosphamide and intravenous immune globulin have been used to reduce inhibitor titers and make ITI more successful.[1] Another immune modulating agent, rituximab, an anti-CD20 monoclonal antibody that inhibits B-cells and interferes with IgG production, has been used with some success. In a phase II trial of rituximab in patients with high titer inhibitors, only 3 out of 16 subjects (18.8%) had a major response (decline in the inhibitor to <5 BU without an increase in the inhibitor titer after rechallenge to factor VIII).[38] When used as a single agent in previously treated patients with inhibitors, rituximab had a modest effect, but further studies are needed to determine the activity of rituximab combined with ITI. Figure 123-1 summarizes the therapeutic options in the management of acute bleeding in patients with hemophilia A and inhibitors.

FIGURE 123-1

Treatment algorithm for the management of patients with hemophilia A and factor VIII antibodies. (aPCC, activated prothrombin complex concentrate; BU, Bethesda unit; PCC, prothrombin complex concentrate.)



Gene Therapy

Hemophilia is an excellent candidate for gene therapy because tight control of gene expression is not required. Even low levels of factor expression can reduce bleeding episodes in patients with severe hemophilia, which is similar to the rationale for prophylactic factor replacement. The goal of gene therapy is to achieve a sustainable factor activity level of over 5% (0.05 units/mL), which is sufficient to convert patients with severe disease to a much milder phenotype.[39,40] If a treatment strategy could produce consistent factor activity levels of around 50% (0.5 units/mL), it would be considered curative.[40] Potential benefits to gene therapy include patient convenience, viral safety, and decreased cost. Possible drawbacks to gene therapy include a risk of inhibitor formation, tumorigenesis related to possible integration of the viral vector, possible germline transmission of the viral vector, and concerns about long-term gene expression.

Gene therapy for the treatment of hemophilia remains in the early clinical stages. Advances are most apparent in hemophilia B, which has been attributed to the smaller size (about 1.4 kb) of its complementary DNA (cDNA).[40] A landmark clinical trial reported the results of a single peripheral venous infusion of an adenovirus associated factor IX transgene vector under the control of a liver-restricted promoter in six patients with severe hemophilia B.[41] All of the study subjects showed long-term (over 2 years) expression of the factor IX transgene with therapeutic levels of factor IX (plateau factor IX levels from 1% to 6% [0.01-0.06 units/mL]).[41]

Gene therapy for factor VIII deficiency has been challenging due to the considerably larger size of its cDNA (about 9 kb).[40] The development of B-domain deleted factor VIII has been beneficial in allowing a smaller amount of cDNA to be able to be packaged into a single vector. A multi-year follow-up of the original clinical trial of Adeno-associated virus (AAV) serotype 5 human factor VIII (hFVIII) SQ (valoctocogene roxaparvovec) was published reporting safety and efficacy data for up to 3 years in the original 15 patients enrolled in this dose escalating study. Patients were enrolled into four escalating dose cohorts. All patients experienced at least one adverse drug reaction; however, all of these were considered mild and transient. No participants dropped out of the study. After 3 years of follow-up one patient had factor VIII levels in the non-hemophilic range, 11 patients had levels in the mild hemophilic range, one patient in the moderate hemophilic range, and two patients (dose level one and dose level two) still have factor VIII levels in the severe hemophilic range. So far this 3-year follow-up does show that the decline in factor levels over time does decrease. No cellular immune response was consistently detected against factor VIII or the AAV serotype 5 capsid in any patient. No factor VIII inhibitors or other antibodies directed to components of factor VIII have been detected in any of the patients.[40]

Other areas of gene therapy are being explored for the treatment of hemophilia. Platelets derived from hematopoietic stem cells may be able to deliver

factor VIII or IX directly into the circulation. Lentiviral vectors are being explored for gene therapy due to their much larger packaging capacities compared to the adeno-associated viral vector AAV. The area of gene editing is also being explored for patients with hemophilia using zinc finger nucleases or clustered regularly interspaced short palindromic repeats (CRISPR) approaches.[41]

Pain Management

Pain, both acute and chronic, can be a common occurrence in patients with hemophilia. The most likely cause of acute pain is bleeding, and treatment should include factor replacement to stop the bleeding, and PRICE (Protect, Rest, Ice, Compression, and Elevation).[1,42] Acetaminophen can be used for mild pain, although narcotic analgesia may be required for more severe pain. NSAIDs impair platelet function and may complicate bleeding. For this reason, nonspecific NSAIDs are not routinely recommended during acute bleeding episodes. Cyclooxygenase-2 inhibitors have less antiplatelet activity and are an option for acute and chronic pain management.[1,42]

Chronic pain in patients with hemophilia is typically secondary to hemophilic arthropathy. Hemophilic arthropathy is the direct result of recurrent hemarthrosis. Persistent blood in the joint leads to inflammation, synovial hypertrophy and inflammation, cartilage destruction, and finally bony erosion. Cyclooxygenase-2 inhibitors can also help manage chronic pain. Surgical interventions may help to alleviate chronic pain. Synovectomy (removal of the hypertrophied synovium) can reduce chronic pain from recurrent bleeding. Patients with more advanced joint disease could benefit from joint replacement.

Surgery

In patients with severe hemophilia, the dose of replacement factor required in the perioperative period will depend on the surgery, the inhibitor status, and the patient's previous response to factor products. Ideally, the patient's factor activity level should be maintained in the range of 50% to 100% (0.5-1.0 units/mL) depending on clinical status and type of procedure. Intermittent dosing or continuous infusion factor replacement may accomplish this goal.[1,32,43] Before surgery, factor concentrate is usually infused to obtain a plasma level of 1 unit/mL (100%). Replacement therapy is continued to maintain plasma levels greater than 0.5 units/mL (50%) for 5 to 7 days or longer, depending on the type of surgery and the patient's clinical response. Preoperative evaluation for elective procedures should include measurement of an inhibitor titer no longer than 2 weeks prior to procedure and assessment of the recovery and half-life of infused factor in the patient.[1] For those patients with inhibitors undergoing surgical procedures, there is evidence to support the use of both activated factor VII and aPCCs.[1,32]

Evaluation of Therapeutic Outcomes

The main goal in the treatment of hemophilia is to control and prevent bleeding episodes and their long-term sequelae such as chronic arthropathies. Pharmacologic and nonpharmacologic interventions should be aimed at achieving this goal. Treatment response can be monitored through clinical parameters such as cessation of bleeding and resolution of symptoms. Monitoring plasma factor levels also may be helpful, particularly for severe bleeding episodes. Home therapy for administration of factor concentrates is common among patients with hemophilia because this approach can lead to earlier treatment and more independence for the patient. Diaries in which the patient documents symptoms, the dose of factor replacement, adjuvant therapies used, and treatment response can help the caregiver to evaluate the success of home therapy. Monitoring the number and type of bleeding episodes and trough plasma factor levels can evaluate the adequacy of prophylactic regimens. Pharmacokinetically driven dosing for prophylactic factor could optimize therapy, reduce bleeding, and decrease overall factor consumption for the patient.[44] Physical examination with evaluation of joint range of motion and radiographic imaging of target joints can evaluate the long-term success of preventing and treating arthropathies.[44]

Clinicians should check for the development of inhibitors, especially in patients with severe disease and exposure to factor concentrates, at least yearly and with any suspicion of poor treatment response. The development of inhibitors challenges the management and control of bleeding episodes. A full understanding of the clinical situation and the titer of the inhibitor are mandatory to address all treatment options for each patient. Because no laboratory test measures the effectiveness of bypassing therapy in patients with inhibitors, close clinical monitoring for worsening or resolution of symptoms is essential for optimizing the outcome.[1]

VON WILLEBRAND DISEASE

von Willebrand disease (vWD) is the most common congenital bleeding disorder in the United States and in the world, with a prevalence of 0.1% to 1%.[45] vWD refers to a family of disorders caused by a quantitative and/or qualitative defect of vWF, a glycoprotein that plays a role in both platelet aggregation and coagulation (Table 123-4). vWF mediates platelet adhesion to injured blood vessel sites and promotes platelet aggregation. It binds factor VIII and protects it from degradation by plasma proteases, thus prolonging its half-life. Unlike hemophilia, vWD has an autosomal inheritance pattern, resulting in an equal frequency of disease in males and females. Diagnosis of vWD may be more prevalent in females due to female-specific hemostatic challenges, such as child birth and menstruation.

TABLE 123-4

von Willebrand Disease—Blood Tests

von Willebrand factor (vWF)
Large multimeric glycoprotein that is necessary for normal platelet adhesion, normal bleeding time, and stabilization of factor VIII
von Willebrand factor antigen (vWF:Ag)
Antigenic determinant(s) on vWF measured by immunoassays; usually low in types 1 and 2; virtually absent in type 3
Ristocetin cofactor activity (RCo)
Functional assay of vWF activity based on platelet aggregation with ristocetin. Reduced by the same degree as vWF:Ag in types 1 and 3, but to a greater extent in type 2 disease (except 2B)
Glycoprotein Ib with gain-of-function mutation (vWF:GPIbM)
Functional assay of vWF binding to a fragment of recombinant glycoprotein Ib; usually low in types 1 and 2; virtually absent in type 3
Glycoprotein Ib with ristocetin-dependent binding (vWF:GPIbR)
Functional assay utilizing ristocetin, recombinant glycoprotein Ib fragments, and microparticles, rather than whole platelets; usually low in types 1 and 2; virtually absent in type 3

Transcription and translation produce a large primary product that subsequently undergoes complex modifications, resulting in vWF multimers of various sizes. vWF is synthesized in endothelial cells, where it is either stored in Weibel–Palade bodies or secreted constitutively. It is also synthesized in megakaryocytes and stored in α-granules, from which it is released following platelet activation.[46,47]

vWF is important for both primary and secondary hemostasis. In response to vascular injury, it promotes platelet adhesion by interacting with the glycoprotein Ib receptor on platelets.[47] It can facilitate platelet aggregation by binding to the platelet glycoprotein IIb/IIIa receptor, although fibrinogen is the main ligand for this receptor.[48] The highest-molecular-weight vWF multimers are the most important in platelet adhesion because their large surface area contains numerous binding sites for various ligands and receptors. vWF is also the carrier molecule for circulating factor VIII, protecting it from premature degradation and removal.[46,47] A deficiency of vWF reduces the half-life of factor VIII and decreases plasma factor VIII levels. Therefore, vWF plays a dual role in hemostasis, affecting both platelet function and coagulation.

Classification of von Willebrand Disease

vWD consists of a heterogeneous group of disorders that can be classified into three major subtypes. The National Institutes of Health has developed a classification scheme that characterizes vWD according to both the quantity of the von Willebrand clotting factors and their functionality (Fig. 123-2). Types 1 and 3 are associated with quantitative defects in vWF; type 2 mutations refer to functional abnormalities in vWF (qualitative defects).[45,47,48] It is important to determine disease subtype because it influences treatment.

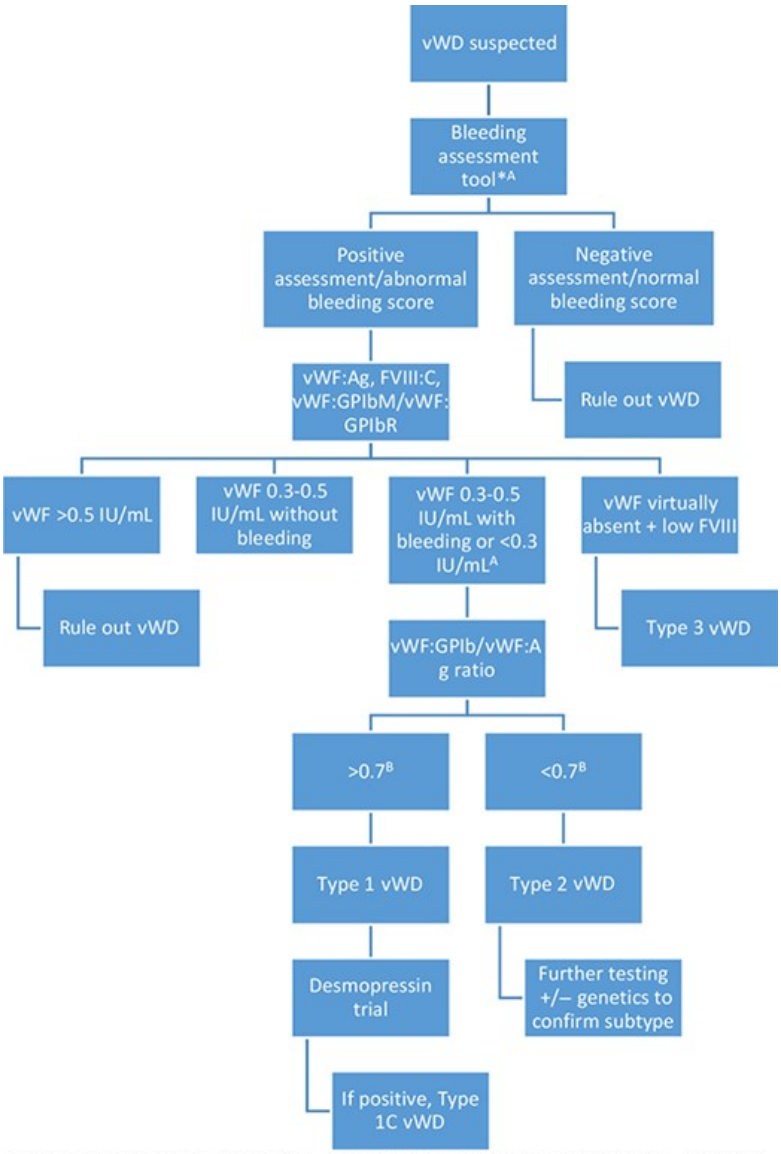
FIGURE 123-2

Classification and Diagnosis of vWD. *Patients with an intermediate or strong probability of vWD should not rely on bleeding assessment tools to guide blood specific testing.

Guideline recommendations:

A = Strong recommendation. Most individuals should follow the recommended course of action. Decision-making tools are not likely to be needed to help patients make decisions which align with their beliefs.

B = Conditional recommendation. Different choices will be appropriate for different patents. Decision aids may be helpful to ensure clinical management aligns with values, preferences, and acceptable risks. *(Adapted from James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of vonWillebrand disease. Blood Adv. 2021;5(1):280–300.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Type 1 vWD is the most common type, accounting for 70% to 85% of cases.[48,49] It is characterized by a mild-to-moderate quantitative reduction in the level of vWF (although its multimeric structure is normal) and a similar reduction in the level of factor VIII. It usually is inherited in an autosomal dominant fashion with variable penetrance and expression.[47] Bleeding symptoms often are very mild to moderate.[47] Patients with vWD can experience mucocutaneous bleeding, such as nosebleeds, bruising, gastrointestinal, or menstrual bleeding. Subjects may be at risk of bleeding following surgery, traumatic injury, or childbirth.[47] Type 1C vWD is characterized by increased clearance of vWF and may be identified by a desmopressin trial (preferred), or measuring the ratio of vWF propeptide to antigen.[45]

Type 2 vWD, diagnosed in 20% to 30% of affected patients, is characterized by a qualitative abnormality of vWF.[50] Bleeding manifestations may be more

severe than with type 1 disease. Inheritance most often is autosomal dominant but may be recessive.[47] Type 2 vWD can be subdivided into four variants. Type 2A is the most frequent subtype and is characterized by a reduced vWF–platelet interaction and an absence of high- and intermediate-molecular-weight factor multimers. Type 2B is a less common variant characterized by an abnormal vWF that has an increased affinity for the platelet glycoprotein Ib receptor. This subtype is associated with thrombocytopenia, which is usually mild. In addition, high-molecular-weight forms of vWF are usually absent. A platelet-type pseudo-vWD has been characterized in which vWF is normal but a defect in the platelet glycoprotein Ib receptor causes an increased affinity for normal vWF.[47] As a result, platelet-type pseudo-vWD is phenotypically similar to type 2B disease but should be distinguished from it because the treatment is different. Type 2M arises from a qualitative defect in vWF that impairs its binding to platelets; it is similar to type 2A, except there is no measurable reduction in the high-molecular-weight multimers.[47] Finally, type 2N vWD (Normandy) is a rare form of the disease in which vWF has a markedly reduced affinity for factor VIII. This subtype leads to a moderate-to-severe reduction of factor VIII plasma levels with normal vWF levels.[47]

Type 3 vWD refers to a severe quantitative variant of the disease in which vWF is nearly undetectable and factor VIII levels are very low (<20 IU/dL [0.2 IU/mL]). Genetic defects in the vWF gene are null alleles in 80% of patients with type 3 disease, supporting the severe lack of vWF in this subtype.[50] Type 3 vWD is rare and accounts for less than 5% of all cases.[50] The clinical phenotype is severe, reflecting major deficits in primary hemostasis and coagulation.

Acquired von Willebrand Syndrome is a rare bleeding disorder that is similar to the congenital form of the disease. It is primarily associated with autoimmune disorders, such as systemic lupus erythematosus, lymphoproliferative disorders, myeloproliferative disorders, cardiovascular diseases, and certain neoplastic diseases, such as Wilms' tumor and lymphoma.[49] Certain medications have been associated with acquired vWD, most notably valproic acid, griseofulvin, and ciprofloxacin.[51,52] Bleeding manifestations vary from mild to severe, and the condition often resolves with treatment of the underlying disease. Various mechanisms have been proposed, including autoantibodies to vWF resulting in rapid removal from the plasma, adsorption to tumor cells or activated platelets, increased proteolysis, or mechanical destruction.[49]

Clinical Presentation and Diagnosis

CLINICAL PRESENTATION: Von Willebrand Disease

Signs and Symptoms

- Clinical manifestations are variable; some patients are asymptomatic
- Mucocutaneous bleeding: epistaxis, gingival bleeding with minor manipulation, menorrhagia
- Easy bruising
- Abnormal bleeding after surgery, childbirth, or dental procedures
- Severe cases: musculoskeletal bleeding

Two evidence-based guidelines regarding vWD were updated in early 2021; one focusing on diagnosis and the other on treatment (discussed later). The American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the WFH formed a multidisciplinary panel to investigate and prioritize clinical questions and outcomes, assess current evidence, and make recommendations.[45]

When a patient has a lifelong history of mucocutaneous bleeding and a family history of abnormal bleeding, vWD should be suspected. A bleeding assessment tool (BAT) should be utilized as a screening measure to determine if a patient warrants specific blood testing for vWD. Many BATs exist, and there is not one recommended over another in the current guidelines.[45] Abbreviated examples of questions which may be included in a BAT are listed in Table 123-5. For patients with a low probability of vWD, such as those seen in a primary care setting, a BAT is recommended for initial screening. A positive bleeding assessment should determine specific blood testing over nonstandardized clinical assessment.[45] For patients with an intermediate

probability of vWD, for example, those referred to hematology, current guidelines recommend against relying on a BAT to determine specific blood testing for diagnosis.[45] Several different laboratory tests are helpful in the diagnosis of this hemostatic abnormality.

TABLE 123-5

Questions to Ask Patients—Bleeding Assessment Tools

Have you ever experienced epistaxis?
• If so, was it spontaneous?
• What interventions were required?
• When and how often did you experience these symptoms?
Have you ever experienced easy/frequent bruising, ecchymosis, or other cutaneous bleeding?
• If so, how often has this occurred?
• What medical interventions were required?
• Where was the location and size of the bleed?
Have you ever experienced prolonged bleeding from minor wounds?
• If so, did you require medical management? Please describe the intervention(s).
Have you ever experienced hematuria and/or gastrointestinal bleeding?
• If so, specify the type of bleeding (hematuria, melena, hematochezia, etc.).
Have you experienced bleeding in the oral cavity (gum bleeding, spontaneous or minor manipulation)?
• How often does this occur and when did it begin?
• Have you required medical management? If so, please describe.
Have you experienced menorrhagia?
• What medical intervention has been required?
• At what age did this symptom begin?
Have you experienced post-partum hemorrhage?
• How long after birth did this symptom occur?

Specific laboratory tests for the diagnosis of vWD include measurement of vWF antigen (vWF:Ag) level, factor VIII assay, determination of vWF ristocetin cofactor (vWF:RCo) activity, and vWF multimer analysis (see Table 123-4). Unfortunately, these levels vary considerably and often indeterminate or

unreliable results can lead to confusion in the diagnosis. For example, the cutoff normal values for vWF:Ag, vWF:RCo, and other specialized tests vary between laboratories. This coupled with the natural variation of plasma concentrations of vWF can complicate interpretation of these results.[47] Plasma concentrations of vWF increase with age, stress, cigarette smoking, exercise, pregnancy starting in the second trimester, infection, and with the use of certain medications such as corticosteroids, high-dose estrogen oral contraceptives, and desmopressin. Repeated test measurements may be necessary due to this physiologic variability.[47]

Electroimmunoassay, immunoradiometric assay, or enzyme-linked immunosorbent assay, or ELISA, can be used to quantify vWF:Ag.[47] vWF:Ag levels are known to vary with different ABO blood types. Individuals with type O blood exhibit up to a 25% decrease in vWF levels when compared to those with type A due to increased plasma protein clearance.[47] The vWF:Ag level is usually low in types 1 and 2 vWD and virtually absent in type 3 disease. Factor VIII levels are normal or mildly decreased in patients with type 1 or 2 disease and very low (<10% [0.1 units/mL]) in those with type 3 disease.[47]

Ristocetin, an antibiotic that causes platelet aggregation in the presence of functional vWF, is used to measure vWF activity. The Ristocetin cofactor activity usually is reduced in parallel to vWF:Ag levels in types 1 and 3 disease and decreased to a greater extent than vWF:Ag in type 2 disease (except type 2B).[47] Low-dose ristocetin-induced platelet agglutination is useful for further distinguishing type 2B disease, as a low concentration of ristocetin induces excessive aggregation in type 2B disease.[47] When this measure is used, there is the potential for false results due to defects in vWF's ability to bind ristocetin due to genetic variants in the vWF gene.[48,54]

Newer, platelet-dependent assays are now recommended over the vWF:RCo activity test due to their lower coefficients of variation and higher reproducibility. Because glycoprotein Ib binding activity is reduced in most types of vWD, this measurement can guide diagnosis. The first assay functions independently of ristocetin and instead introduces gain-of-function mutations to GPIbα (glycoprotein Ib alpha), therefore allowing it to bind vWF in vitro, spontaneously. The vWF:GPIbM assay provides greater precision with lower limits of detection compared to previous tests but is available.[48,55] Another assay still utilizes ristocetin, but also incorporates recombinant glycoprotein Ib fragments adhered to microparticles, rather than whole platelets. This assay may be susceptible to similar genetic variants as the vWF:RCo assay; however, greater sensitivity and less variation have been observed.[54]

vWF, secreted as high-molecular-weight multimers, is cleaved in plasma to increasingly small protein fragments. The distribution of these multimer sizes can help determine the type of vWD. All multimer sizes are present in type 1 disease, whereas reduced levels of intermediate- and high-molecular-weight multimers are characteristic of type 2 disease. Patients with type 3 disease lack all sizes of vWF multimers. Molecular genetic testing for vWD is now a feasible option in some instances. Genetic testing may clarify diagnostic uncertainty that may remain after coagulation testing and clinical evaluation, and may be especially useful in diagnosing type 2B and 2N vWD.[45,47] Figure 123-2 illustrates the diagnostic algorithm recommended by the guidelines for types 1 and 2 vWD. Type 3 vWD is not addressed in the most recent guidelines, as diagnosis is relatively straight forward for these patients. vWF is virtually absent in type 3 disease (<3 IU/dL [0.03 IU/mL]), with an associated low FVIII level.

Treatment: von Willebrand Disease

6 The specific type of vWD and the location and severity of bleeding determine the approach to treatment. The guidelines from ASH, ISTH, NHF, and WFH cover recommendations ranging from prophylaxis in severe disease to heavy menstrual bleeding.[53] The comprehensive care of patients with vWD requires an interprofessional team approach. The desired outcome is to prevent bleeding episodes and their short-term and long-term consequences so that patients with vWD can live active and productive lives. Local measures, including prolonged pressure, ice, and topical thrombin, often can control superficial bleeding. Systemic treatment is used for bleeding that cannot be controlled in this manner and for the prevention of bleeding with surgery. The goal of systemic therapy is to correct platelet adhesion and coagulation defects by stimulating the release of endogenous vWF or by administering products that contain vWF and factor VIII or vWF alone.[53] General guidelines for the treatment of vWD are shown in Table 123-6.

TABLE 123-6

Management Recommendations—ASH–ISTH–NHF–WFH Guidelines

Clinical Question	Recommendation	Strength of Recommendation
Prophylaxis	In vWD with severe and frequent bleeds, long-term prophylaxis is suggested, rather than no prophylaxis.	Conditional
Desmopressin trial and administration	If desmopressin in an option (primarily Type 1) and vWF <0.30 IU/mL, trial of desmopressin is suggested. The panel suggests against treating with desmopressin in the absence of a trial first.	Conditional
Antithrombotic therapy	In patients with vWD and cardiovascular disorders requiring anticoagulants or antiplatelet agents, use of these agents is suggested over no therapy.	Conditional
Major surgery	Target vWF and FVIII activity levels ≥0.50 IU/mL for at least 3 days after surgery.	Conditional
Minor surgery/invasive procedures	Target vFW activity levels ≥0.50 IU/mL using desmopressin or factor concentrate along with tranexamic acid.	Conditional
Gynecology—heavy menstrual bleeding	Hormonal therapy or tranexamic acid is suggested over desmopressin.	Conditional

Abbreviated recommendations from the 2021 Guidelines on treatment of vWD. Additional recommendations can be found in the source document. Strength of Recommendations: *Strong:* Most individuals should follow the recommended course of action. Decision-making tools are not likely to be needed to help patients make decisions which align with their beliefs. *Conditional:* Different choices will be appropriate for different patents. Decision aids may be helpful to ensure clinical management aligns with values, preferences, and acceptable risks. *(Data from Reference 53.)*

Replacement Therapy

7 The treatment of choice for patients with severe vWD, including types 2B, 2M, and 3 vWD and for patients with type 1 or 2A vWD who are unresponsive to desmopressin, is replacement therapy with vWF concentrate.[53] Several virus-inactivated, intermediate- or high-purity plasma-derived factor VIII concentrates contain sufficient amounts of functional vWF for treatment in this patient population (see Table 123-2). Ultrahigh-purity (monoclonal antibody-derived) plasma-derived products contain only negligible amounts of vWF and recombinant factor VIII products contain no vWF and are inadequate for treatment of vWD. The evolution of replacement therapy over the past several decades has improved the therapy options available to patients, particularly with severe disease.[56]

Recombinant vWF alone was approved by the US Food and Drug Administration (FDA) in 2015 for on-demand treatment and control of bleeding episodes as well as perioperative management of bleeding in patients with vWD. Unlike plasma-derived vWF, recombinant products have no exposure to the ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13) which cleave large multimers.[57] Ultralarge and high-molecular-weight multimers are necessary for optimal platelet plug formation, making recombinant products ideal.[56,57]

Cryoprecipitate was one of the earliest forms of replacement therapy for vWD. It contains about 80 to 100 units of vWF per unit (5-10 times more vWF and factor VIII than fresh-frozen plasma), and it was the mainstay of therapy for vWD. However, because cryoprecipitate is not always virally inactivated, it should not be used as first-line treatment and is no longer recommended in the United States or Europe.[56]

Other Pharmacological Therapy

Desmopressin stimulates the endothelial cell release of vWF and factor VIII. It is temporarily effective for patients with vWD who have adequate endogenous stores of functional vWF, which includes most patients with type 1 disease and some patients with type 2A disease. Conversely, desmopressin is not appropriate for patients with type 3 disease, who lack stores of vWF. Desmopressin usually is not recommended for the treatment of type 2B disease because the release of additional abnormal vWF may exacerbate thrombocytopenia, but it has been reported to be beneficial in some patients with type 2B disease.[58] If desmopressin is used for the treatment of type 2B disease, close monitoring is necessary.

The dose of desmopressin used for treatment of vWD is identical to that used for treatment of mild factor VIII deficiency, 0.3 mcg/kg given IV over 15 to 30 minutes.[15] Patients with vWD generally have a better response to desmopressin than those with hemophilia, with an average three- to fivefold increase in vWF and factor VIII levels.[48] These levels remain elevated for about 6 to 8 hours. The response to desmopressin in a given patient usually is consistent, and a desmopressin trial should determine if the medication likely will be effective for the individual. Desmopressin is preferable to use of plasma-derived products for patients who have an adequate response because desmopressin does not carry a risk of viral transmission. An added benefit is the substantially lower cost of desmopressin compared to the plasma-derived and recombinant products. (For a discussion of the adverse drug reactions of desmopressin, see "Hemophilia: Other Pharmacologic Therapy" section.)

Desmopressin can be administered every 12 to 24 hours, but the response diminishes with repeated treatment. After three to four doses, desmopressin often is no longer effective and alternative replacement therapy may be necessary if prolonged treatment is required. Laboratory monitoring, including vWF:Ag measurements, factor VIII assays, vWF:activity assessments, and clinical examinations, will determine the adequacy of treatment.[58] Intranasal administration of desmopressin, at the same dosage as that used for mild factor VIII deficiency, can be useful for the treatment of mild bleeding episodes. One or two doses administered at the start of menses may help control menorrhagia. Oral contraceptives may also be very effective in controlling this symptom (see Table 123-6). Antifibrinolytic agents, such as aminocaproic acid and tranexamic acid, may be of special value in bleeds associated with tissues rich in plasminogen activators, such as the mouth, especially with tooth extractions.[58] These agents can also be used in the management of epistaxis, GI bleeding, and menorrhagia. However, these agents should be avoided in urinary tract bleeding because of the risk of thrombosis and obstruction.

In acquired vWD, low levels of plasma vWF are the result of accelerated removal of protein from plasma through the action of different pathogenic mechanisms. Acquired vWD may be associated with monoclonal gammopathy, lymphoproliferative or myeloproliferative syndromes, or autoimmune disorders. Cardiovascular disease, such as aortic stenosis and congenital cardiac defects, are increasing in the literature as causes of acquired vWD. Intravenous immune globulin remains a therapeutic option in acquired vWD, along with vWF concentrate and/or desmopressin.[51]

Gene Therapy

Patients with the most severe bleeding phenotypes of vWD (type 3 and some severe cases of types 1 and 2) may be the most likely candidates for gene therapy, which offers the potential of a long-term, if not lifelong, correction of vWF deficiency. Preclinical trials are being conducted to test the feasibility of gene transfer in the management of vWD.[59]

Evaluation of Therapeutic Outcomes

Since the main goal in the treatment of vWD is to prevent or control bleeding and the consequences of such bleeding, bleeding episodes can be monitored via clinical and laboratory parameters. Monitoring the number and types of bleeding episodes and measurement of plasma concentrations of vWF and factor VIII make it possible to evaluate the effectiveness of specific prophylactic and treatment regimens. As with hemophilia patients, assessment of patients' activities of daily living gives clinicians a better appreciation of the success of the treatment plan.

OTHER CONGENITAL FACTOR DEFICIENCIES

Rare bleeding disorders constitute 3% to 5% of all inherited coagulation factor deficiencies.[60] These rare bleeding disorders include congenital deficiencies in fibrinogen, in factors II, V, VII, X, XI, and XIII, and in combinations of factor deficiencies. Contact factor abnormalities, including deficiencies in factor XII, high-molecular-weight kininogen, and prekallikrein, prolong the aPTT but do not lead to any bleeding diathesis. Identification of these disorders is important so that inappropriate treatment is not given. The only contact factor deficiency associated with bleeding symptoms is factor XI deficiency. Also known as hemophilia C, this deficiency is particularly common in people of Ashkenazi Jewish descent.[61] Bleeding

manifestations are variable. Bleeding usually does not occur spontaneously, but excessive bleeding may occur after trauma or surgery. Most other deficiencies are inherited as autosomal recessive disorders and are rare. Some patients with abnormal molecules, such as a dysfibrinogenemia, may have an increased tendency to develop thromboembolic disease. Most of these deficiencies are treated with fresh-frozen plasma. Newer specific concentrates are becoming available. For example, a factor XIII plasma-derived concentrate is available, and recombinant factor VIIa is approved for use in patients with congenital VII deficiency. Cryoprecipitate, which is rich in fibrinogen, or fibrinogen concentrates (RiaSTAP®), can be used to treat patients with fibrinogen deficiency or dysfunctional fibrinogen (dysfibrinogenemia).

COMPLICATIONS OF REPLACEMENT THERAPY

As discussed previously, the transmission of blood borne infectious diseases is a concern when blood and blood-derived products are used. Most patients with hemophilia who received plasma-derived products were infected with hepatitis viruses and HIV during the 1980s prompting the development of viral inactivation methods for use during the manufacturing of factor concentrates.[15] All available plasma-derived factor concentrates come from screened donors and undergo viral inactivation procedures in an effort to reduce the risk of viral transmission. Heat treatment, which includes dry and wet heat, is one method of viral inactivation. Wet heat is applied while the concentrate is in suspension or in solution (pasteurization) and is more effective than dry heat. Other methods of viral inactivation include chemical (solvent detergent) and affinity chromatography with monoclonal antibodies. Solvent detergent treatment inactivates lipid-coated viruses, such as HIV and hepatitis B and C, but it is not effective against parvovirus B19, transfusion transmitted virus, hepatitis A, or prions.[5] Parvovirus B19 is found in both plasma-derived and recombinant factor VIII concentrates (due to the use of albumin as a stabilizer in some recombinant products).[5,19] Parvovirus B19 may be particularly important for patients with hemophilia and HIV infection because it can cause chronic anemia in patients with immune deficiency.

Other complications associated with factor administration include allergic reactions, fever, chills, urticaria, and nausea. PCCs and aPCCs also have the potential to cause thromboembolic complications, including deep-vein thrombosis, pulmonary embolism, myocardial infarction, and disseminated intravascular coagulation, likely related to the presence of activated factors.[15] Antifibrinolytic agents should not be given to patients receiving PCCs or aPCCs to avoid thrombotic complications.

Porcine factor VIII, used in the treatment of patients with inhibitors to factor VIII, is not known to transmit human viruses. However, allergic-type reactions (eg, fever, chills, skin rashes, nausea, and headaches) have been reported.[15] Patients who experience these reactions can be treated with steroids and/or diphenhydramine. Thrombocytopenia is another potential complication of porcine factor VIII use.[15]

CONCLUSION

Coagulation disorders, such as hemophilia and vWD, affect a small subset of the overall population, but their treatment can be costly and complicated, requiring knowledgeable health professionals and an interprofessional team approach for optimal outcomes to be achieved. Exciting progress is being made in the development of new strategies for treating these types of disorders. The development of new factor products with improved pharmacokinetic properties, non-factor replacement therapy, as well as the advances in gene therapy may soon redefine the therapeutic landscape for these patients and improve their overall experience.

ABBREVIATIONS

AAV	adeno-associated virus
ADAMTS13	a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
ASH	American Society of Hematology
BAT	bleeding assessment tool
BU	Bethesda unit
cDNA	circulating DNA
HIV	human immunodeficiency virus
IgG	immunoglobulin G
ISTH	International Society on Thrombosis and Haemostasis
ITI	immune tolerance induction
NHF	National Hemophilia Foundation
NSAID	nonsteroidal anti-inflammatory drug
PCC	prothrombin complex concentrate
PRICE	Protect, Rest, Ice, Compression, and Elevation
SIPPET	Survey of Inhibitors in Plasma-Product Exposed Toddlers
vWD	von Willebrand disease
vWF	von Willebrand factor
vWF:Ag	von Willebrand factor antigen
vWF:RCo	von Willebrand factor ristocetin cofactor
vWF:GPIbM	von Willebrand factor glycoprotein Ib mutational assay
WFH	World Federation of Hemophilia

REFERENCES

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia.* 2013;19:e1–e47. [PubMed: 22776238]

2. Wynn TT, Gumuscu B. Potential role of a new PEGylated recombinant factor VIII for hemophilia. *J Blood Med.* 2016;7:121–128. [PubMed: 27382347]

3. World Federation of Hemophilia. Carriers and Women with Hemophilia. 2012. Available at: http://www1.wfh.org/publication/files/pdf-1471.pdf.

4. Shahriari M, Bazrafshan A, Moghadam M, Karimi M. Severe hemophilia in a girl infant with mosaic Turner syndrome and persistent hyperplastic primary vitreous. *Blood Coagul Fibrinolysis.* 2016;27:352–353. [PubMed: 26484646]

5. Lee C, Berntorp E, Hoots W, eds. *Textbook of Hemophilia.* 3rd ed. Chichester, West Sussex, UK: Wiley-Blackwell; 2014.

6. Structural Immunology Group, University of College London. Factor VIII (F8). 2021. Available at: http://www.factorviii-db.org.

7. Structural Immunology Group, University of College London. Factor IX Gene (F9). 2021. Available at: https://www.factorix.org/.

8. Funnell APW, Crossley M. Hemophilia B Leyden and once mysterious cis-regulatory mutations. *Trends in Genetics.* 2014;30:18–23.

9. Davies GA, Poon MC, Rydz N, Goodyear D. Attitudes toward prenatal diagnosis and pregnancy management in carriers of hemophilia: A qualitative analysis exploring the views of carriers in Southern Alberta. *Blood.* 2016;128:4742.

10. Xu XP, Gan HY, Li FX, et al. A method to quantify cell-free fetal DNA fraction in maternal plasma using next generation sequencing: Its application in non-invasive prenatal chromosomal aneuploidy detection. *PLoS ONE.* 2016;11:1–13.

11. Carpenter SL, Soucie JM, Presley MV, et al. Hepatitis B vaccination is effective by subcutaneous route in children with bleeding disorders: A universal data collection database analysis. *Haemophilia.* 2015;21:e39–e43. [PubMed: 25381731]

12. Streif W, Knöfler R. Perinatal management of haemophilia. *Hämostaseologie.* 2020;40:226–232. doi: 10.1055/a-1141-1252.

13. Acharya SS. Advances in hemophilia and the role of current and emerging prophylaxis. *Am J Manag Care.* 2016;22:S116–S125. [PubMed: 27266808]

14. Berntorp E, Andersson NG. Prophylaxis for haemophilia in the era of extended half-life factor VIII/factor IX products. *Semin Thromb Hemost.* 2016;42:518–525. [PubMed: 27096762]

15. Lexicomp Online®, Pediatric & Neonatal Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; 2018.

16. Chen SL. Economic costs of hemophilia and the impact of prophylactic treatment on patient management. *Am J Manag Care.* 2016;22(5 suppl):s126–s133. [PubMed: 27266809]

17. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med.* 2017;377:809–818. [PubMed: 28691557]

18. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med.* 2018;379:811–822. [PubMed: 30157389]

19. Aledort LM. The evolution of comprehensive haemophilia care in the United States: Perspectives from the frontline. *Haemophilia.* 2016;22:676–683. [PubMed: 27354149]

20. Berntorp E, Shapiro AD. Modern haemophilia care. *Lancet.* 2012;379:1447–1456. [PubMed: 22456059]

21. Negrier C, Karim FA, Lepatan LM, et al. Efficacy and safety of long-acting recombinant fusion protein linking factor IX with albumin in haemophilia

B patients undergoing surgery. *Haemophilia.* 2016;22:e259–e266. [PubMed: 27333467]

22. Nolan B, Mahlangu J, Perry D, et al. Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with hemophilia A. *Haemophilia.* 2015;22:72–80. [PubMed: 26218032]

23. Dube E, Bonnefoy A, Merien C, et al. A prospective surveillance study of inhibitor development in haemophilia A patients following a population switch to a third-generation B-domain-deleted recombinant factor VIII. *Haemophilia.* 2018;24:236–244. [PubMed: 29388742]

24. Urwin P, Thanigaikumar K, Ironside JW, et al. Sporadic Creutzfeldt-Jakob disease in 2 plasma product recipients, United Kingdom. *Emerging Inf Diseases.* 2017;23:893–897.

25. Micromedex® Healthcare Series. Greenwood Village, CO: Thomson Reuters (Healthcare). Updated September 21, 2021.

26. Prelog T, Dolnicar MB, Kitanovaski L. Low-dose continuous infusion of factor VIII in patients with haemophilia A. *Blood Transfus.* 2016;14:474–480. [PubMed: 26674820]

27. Loomans JI, Kruip MJHA, Carcao M, et al. Desmopressin in moderate hemophilia A patients: A treatment worth considering. *Haematologica.* 2018;103:550–557. [PubMed: 29305412]

28. Shima M, Lillicrap D, Kruse-Jarres R. Alternative therapies for the management of inhibitors. *Haemophilia.* 2016;22:36–41. [PubMed: 27405674]

29. Ljung RCR. How I manage patients with inherited haemophilia A and B and factor inhibitors. *Br J Haematol.* 2018;180:501–510. [PubMed: 29270992]

30. Konkle BA. Impacting inhibitor development in hemophilia A. *Blood.* 2017;130:1689–1690. [PubMed: 29025717]

31. Peyvandi F, Manucci PM, Garagiola I, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. *N Engl J Med.* 2016;374:2054–2064. [PubMed: 27223147]

32. Santagostino E, Escobar M, Ozelo M, et al. Recombinant activated factor VII in the treatment of bleeds and for the prevention of surgery-related bleeding in congenital haemophilia with inhibitors. *Blood Rev.* 2015;29(suppl 1):S9–S18. [PubMed: 26073369]

33. Antunes SV, Tangada S, Stasyshyn O, et al. Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. *Haemophilia.* 2014;20:65–72. [PubMed: 23910578]

34. Mannucci PM, Franchini M. Porcine recombinant factor VIII: An additional weapon to handle anti-factor VIII antibodies. *Blood Transfus.* 2017;15:365–368. [PubMed: 27483484]

35. Valentino LA, Kempton CL, Kruse-Jarres R, et al. US guidelines for immune tolerance induction in patients with haemophilia a and inhibitors. *Haemophilia.* 2015;21:559–567. [PubMed: 26032231]

36. Collins P, Chalmers E, Alamelu J, et al. First-line immune tolerance induction for children with severe haemophilia A: A protocol from the UK Haemophilia Centre Doctors' Organisation Inhibitor and Paediatric Working Parties. *Haemophilia.* 2017;23:654–659. [PubMed: 28574205]

37. Batsuli G, Meeks SL, Herzog RW, et al. Innovating immune tolerance induction for haemophilia. *Haemophilia.* 2016;22(S5):31–35. [PubMed: 27405673]

38. Jiang L, Liu Y, Zhang L, et al. Rituximab for treating inhibitors in people with inherited severe hemophilia. *Cochrane Database Syst Rev.* 2017;7:1465–1858.

39. Giangrande P. The future of hemophilia treatment: Longer-acting factor concentrates versus gene therapy. *Semin Thromb Hemost.* 2016;42:513–

517. [PubMed: 27148842]

40. Pasi KJ, Rangarajan S, Mitchell N, et al. Multiyear follow-up of AAV5-hFVIII-SQ gene therapy for hemophilia A. *NEJM.* 2020;382:29–40. doi: 10.1056/nejmoa1908490.

41. van den Berg HM. A cure for hemophilia within reach. *N Engl J Med.* 2017;377:2592–2593. [PubMed: 29224412]

42. Auerswald G, Dolan G, Duffy A, et al. Pain and pain management in haemophilia. *Blood Coagul Fibrinolysis.* 2016;27:1–10. [PubMed: 26484638]

43. Mensah PK, Gooding R. Surgery in patients with inherited bleeding disorders. *Anaesthesia.* 2015;70(suppl 1):112–120. [PubMed: 25440405]

44. Pasca S, Milan M, Sarolo L, Zanon E. PK-driven prophylaxis versus standard prophylaxis: When tailored treatment may be a real and achievable cost-saving approach in children with severe hemophilia A. *Thrombosis Research.* 2017;157:58–63. [PubMed: 28692842]

45. James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. *Blood Adv.* 2021;5(1):280–300. doi: 10.1182/bloodadvances.2020003265.

46. Swami A, Kaur V. von Willebrand disease: A concise review and update for the practicing physician. *Clin Appl Thromb Hemost.* 2017;23:900–910. [PubMed: 27920237]

47. Ng C, Motto DG, Di Paola J. Diagnostic approach to von Willebrand disease. *Blood.* 2015;125:2029–2037. [PubMed: 25712990]

48. Sharma R, Flood VH. Advances in the diagnosis and treatment of von Willebrand disease. *Blood.* 2017;130:2386–2391. [PubMed: 29187375]

49. Mital A. Acquired von Willebrand syndrome. *Adv Clin Exp Med.* 2016;25(6):1337–1344. doi: 10.17219/acem/64942.

50. Leebeek FWG, Eikenboom JCJ. von Willebrand disease. *N Engl J Med.* 2016;375:2067–2080. [PubMed: 27959741]

51. Franchini M, Mannucci PM. Acquired von Willebrand syndrome: Focused for hematologists. *Haematologica.* 2020;105(8):2032–2037. doi: 10.3324/haematol.2020.255117.

52. Kumar R, Vidaurre J, Gedela S. Valproic acid-induced coagulopathy. *Pediatr Neurol.* 2019;98:25–30. doi: 10.1016/j.pediatrneurol.2019.04.019.

53. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Adv.* 2021;5(1):301–325. doi: 10.1182/bloodadvances.2020003264.

54. Boender J, Eikenboom J, van der Bom JG, et al. Clinically relevant differences between assays for von Willebrand factor activity. *J Thromb Haemost.* 2018;16:2413–2424. doi: 10.1111/jth.14319.

55. Patzke J, Favaloro EJ. Laboratory testing for von Willebrand Factor activity by Glycoprotein Ib Binding Assays (VWF:GPIb). *Methods Mol Biol.* 2017;1646:453–460. doi: 10.1007/978-1-4939-7196-1_33.

56. Peyvandi F, Kouides P, Turecek PL, et al. Evolution of replacement therapy for von Willebrand disease: From plasma fraction to recombinant von Willebrand factor. *Blood Rev.* 2019;38:100572–100572. doi: 10.1016/j.blre.2019.04.001.

57. Gill JC, Castaman G, Windyga J, et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood.* 2015;126:2038–2046. [PubMed: 26239086]

58. Laffan MA, Lester W, O'Donnell JS, et al. The diagnosis and management of von Willebrand disease: A United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *Br J Haematol.* 2014;167:453–465. [PubMed: 25113304]

59. Portier I, Vanhoorelbeke K, Verhenne S, et al. High and long-term von Willebrand factor expression after *Sleeping Beauty* transposon-mediated gene therapy in a mouse model of severe von Willebrand disease. *J Thromb Haemost.* 2018;16:592–604. [PubMed: 29288565]

60. James P, Salomon O, Mikovic D, et al. Rare bleeding disorders—Bleeding assessment tools, laboratory aspects and phenotype and therapy of FXI deficiency. *Haemophilia.* 2014;20:71–75. [PubMed: 24762279]

61. Franchini M, Marano G, Pupella S, et al. Rare congenital bleeding disorders. *Ann Transl Med.* 2018;6:331. [PubMed: 30306070]

SELF-ASSESSMENT QUESTIONS

1. The genetic inheritance pattern for hemophilia is:
   A. Autosomal dominant and more prevalent in males
   B. Autosomal recessive and more prevalent in females
   C. X-linked, therefore affects more females than males
   D. X-linked, therefore affects more males than females
2. The factor deficit in hemophilia B is:
   A. Factor II
   B. Factor VII
   C. Factor VIII
   D. Factor IX
3. Standard of care for patients with severe hemophilia A consists of:
   A. Desmopressin therapy to treat bleeding episodes
   B. Regular administration of a hemostatic agent(s) to prevent bleeding episodes
   C. Administration of activated prothrombin complex concentrates in all patients with active bleeds
   D. On-demand factor therapy to avoid long-term complications
4. Patients with moderate hemophilia have _____ factor activity level.
   A. 1% to 5% (0.01 to 0.05 units/mL)
   B. 1% to 10% (0.01 to 0.1 units/mL)
   C. 5% to 10% (0.05 to 0.1 units/mL)
   D. 10% to 40% (0.1 to 0.4 units/mL)
5. The first-line therapeutic approach to treat an active bleed in a patient with severe hemophilia *with* inhibitors is:
   A. Low-dose factor replacement for patients with low titer inhibitors
   B. Recombinant factor VIII replacement for patients with any level of inhibitors

C. Activated prothrombin complex concentrates (aPCCs) for patients with high titer inhibitors

D. Alternating desmopressin and anti-thrombolytics in any patient with inhibitors

6. Which of the following is a *true* statement regarding prophylaxis therapy for hemophilia?

A. Not recommended by any national organization.

B. Recommended approach but optimal dosing and schedule is not well defined.

C. Proven cost effective.

D. Patient compliance is not a factor in overall outcome.

7. What is the mechanism by which activated prothrombin complex concentrates (aPCCs) overcome inhibitors?

A. aPCCs provide multiple factor products which are known deficits in hemophilia.

B. Vitamin K-dependent factors and small quantities of activated factor products in aPCCs overcome most inhibitor titers.

C. aPCCs provide factor products which bypass the antibodies that inhibitors target.

D. Large concentrations of factor IX and VIII are present in aPCCs and are able to overcome inhibitors.

8. Which of the following is *true* regarding emicizumab?

A. Approved for use in adults with severe hemophilia

B. Acts as a bridge between activated factor IX and factor X

C. Proven effective only in pediatric patients without inhibitors

D. Given subcutaneously one time per month

9. Select the appropriate approach to treating an acute bleed in a patient with hemophilia A with the corresponding inhibitor titer:

A. 8 BU/mL; High dose plasma derived FVIII

B. 7 BU/mL; Activated prothrombin complex concentrates

C. 6 BU/mL; High dose recombinant FVIII

D. <5 BU/mL; Activated prothrombin complex concentrates

10. 10. Though target ranges differ based on risk and clinical status, what is the ideal factor activity level for a patient undergoing a surgical procedure?

A. >5% (>0.05 units/mL)

B. 5% to 40% (0.05 to 0.4 units/mL)

C. 40% to 70% (0.4 to 0.7 units/mL)

D. 50% to 100% (0.5 to 1.0 units/mL)

11. How much does 1 unit/kg of plasma-derived factor IX increase the factor activity level in a patient with hemophilia B?

A. <1% (<0.01 units/mL)

B. 1% (0.01 units/mL)

C. 2% (0.2 units/mL)

D. 50% (0.5 units/mL)

12. What would be the appropriate dose of recombinant factor IX for an adult patient with severe hemophilia B requiring a 50% correction?

A. 25 units/kg

B. 50 units/kg

C. 60 units/kg

D. 70 units/kg

13. Which of the following is a common presentation of von Willebrand disease?

A. Bleeding of the gums after major procedures only

B. Keratoconjuntivitis sicca

C. Delayed bruising

D. Menorrhagia

14. Which of the following factor products can be used to treat severe bleeding episodes in patients with von Willebrand disease?

A. Recombinant von Willebrand factor

B. Recombinant FVIII

C. Plasma-derived FVIII

D. Desmopressin

15. Which of the following is a *true* statement regarding desmopressin?

A. Desmopressin is effective in patients with severe hemophilia A.

B. Desmopressin is effective in patients with severe hemophilia B.

C. Desmopressin exhibits tachyphylaxis with repeated dosing.

D. Desmopressin is effective in all patients with von Willebrand disease.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Both hemophilia A and B are recessive, X-linked diseases, resulting in a higher incidence in males (see "Hemophilia" section).

2. **D.** Hemophilia B, also known as Christmas disease, is the result of a deficiency in factor IX (see "Hemophilia" section).

3. **B.** Prophylaxis is recommended in severe hemophilia, as it reduces bleeding episodes and damage due to recurrent joint bleeds. The agents used for prophylaxis has traditionally been factor concentrates; however, products like emicizumab have helped create a modern definition of prophylaxis (see "Prophylaxis Using Factor Replacement" and "Prophylaxis with Non-factor Products" sections)

4. **A.** Moderate hemophilia is defined as factor activity level of 1% to 5% (0.01 to 0.05 units/mL)(see "Hemophilia" section for clinical manifestations).

5. **C.** Patients with low titer inhibitors may be treated with high-dose factor replacement therapy, while patients with high titer inhibitors require

agents that bypass the factor to which the antibody has formed (see "Treatment of Inhibitors" subsection under "Hemophilia" section and Fig. 123-2).

6. **B.** There is not strong literature to support the dosing and timing of initiation of prophylactic factor therapy. Though primary prophylaxis is an expensive approach, the WFH does recommend it in patients with severe hemophilia. Ideal hemostatic agents used for prophylaxis is becoming more inclusive with regard to mechanisms of action and modalities of administration. (See "Prophylaxis Using Factor Replacement" and "Prophylaxis with Non-factor Products" sections.)

7. **C.** Activated prothrombin complex concentrates (aPCCs) contain greater quantities of activated factor products (namely factor X and prothrombin) which are able to bypass the factor to which the antibody is directed (see "Treatment of Inhibitors" subsection under "Hemophilia" section).

8. **B.** Emicizumab performs the function of activated factor VIII by bridging activated factor IX and factor X (see "Treatment of Inhibitors" subsection under section "Hemophilia" section).

9. **B.** Patients with inhibitor titers <5 BU/mL can generally be treated with high-dose factor replacement therapy. Patients with titers >5 BU/mL require bypassing agents, such as aPCCs (see "Treatment of Inhibitors" subsection under "Hemophilia" section and Fig. 123-1).

10. **D.** The dose of replacement factor required perioperatively will differ between patients. Ideally, the patient's factor activity level should be maintained at 50% to 100% (0.5 to 1.0 units/mL) depending on clinical status and type of procedure (see "Surgery" subsection under "Hemophilia" section and Table 123-3).

11. **B.** For plasma-derived factor IX, each unit/kg of factor results in an increase of about 1% (0.01 units/mL) in the plasma factor activity level. Calculations for recombinant factor products in pediatric and adult patients contain specific multipliers due to the lower recovery of recombinant products compared to plasma-derived products (see "Factor IX Dosing" section).

12. **C.** Use the following equation for adult patients: Recombinant factor IX (units) = (Desired level − Baseline level) × 1.2 × (Weight [in kilograms]) ⟶ 60 units/kg = (50%-0%) × 1.2 (see "Factor IX Dosing" section).

13. **D.** Some patients with von Willebrand disease are asymptomatic. If patients do have symptoms, they often present with mucocutaneous bleeding, menorrhagia, easy bruising, and postoperative bleeding (see "von Willebrand Disease" section and its "Clinical Presentation" subsection).

14. **A.** Recombinant vWF was approved for on-demand treatment and control of bleeding episodes in patients with vWD. While plasma-derived FVIII concentrates contain sufficient amounts of vWF to treat bleeding episodes, recombinant products contain no vWF and are inadequate for treatment (see "Replacement Therapy" subsection under "von Willebrand Disease" section).

15. **C.** Tachyphylaxis occurs on repeated dosing of desmopressin. This drug is not effective in patients with severe hemophilia and some forms of von Willebrand disease (see "Hemophilia," "Other Pharmacologic Therapy," and "von Willebrand Disease" sections).