Hematology-Oncology Board Review Manual

Hemophilia A and B: An Overview

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INTRODUCTION

Hemophilia A and B are the most common severe inherited bleeding disorders. The incidence of hemophilia is 1 in 5000 live male births, with hemophilia A occurring 4 times more commonly than hemophilia B. The associated decrease in factor VIII in hemophilia A was initially identified in 1947, and the decrease in factor IX associated with hemophilia B was identified 5 years later.\(^1,2\) Both conditions are inherited as X-linked recessive traits. Queen Victoria of Britain, who reigned from 1837 to 1901, was a carrier of hemophilia and had 2 carrier daughters, Alice and Beatrice, and a son with hemophilia, Leopold.\(^3\) In 1984 and 1985, the genes for factor VIII and factor IX were cloned, and in 1989 recombinant factor VIII was first used clinically.\(^4-7\)

PATHOPHYSIOLOGY

Both factors VIII and IX are crucial for normal thrombin generation in the coagulation pathway. After any injury, the initial hemostatic event is the formation of a platelet plug. Once the platelet plug is formed, subsequent generation of fibrin prevents continued oozing from the affected site. In hemophilia A and B, the propagation phase of coagulation is impaired, and as a result, the formation of clot is delayed and is not robust. Due to the delayed formation of an abnormal clot, patients with hemophilia do not bleed rapidly but rather ooze continuously. Rebleeding is a common occurrence in inadequately treated patients.\(^8\)

GENETICS

The gene for factor VIII (\(F8\)) is located in the most distal band (Xq28) of the long arm of the X chromosome. Spanning more than 186 kb, it is one of the largest genes known.\(^9,10\) The gene for factor IX (\(F9\)) is located at Xq27.1 and spans 33 kb.\(^7\) Defects in the \(F8\) gene associated with hemophilia A may be divided into several categories: gross gene rearrangements; insertions or deletions of genetic sequence of a size varying from 1 base pair up to the entire gene; or single DNA base substitutions resulting in either amino acid replacement (missense), premature peptide chain termination (nonsense, or stop mutations), or mRNA splicing defects. All classes of defects can result in severe disease. However, the single most clinically important defect is a gene rearrangement (an inversion) involving \(F8\) intron 22, which results in approximately 50% of all severe hemophilia A cases worldwide.\(^11,12\) In hemophilia B, point mutations are by far the most common type of abnormality. Generally, they are caused by DNA polymerases adding the wrong nucleotide during replication.\(^13\)

HEMOPHILIA IN FEMALES

X-Inactivation (also called Lyonization) is a process that occurs early in embryonic development in female mammals where 1 of the 2 copies of the X chromosome present is inactivated; it is the reason why some female carriers of hemophilia can become symptomatic. Approximately one third of carriers have clotting factor levels of less than 60% of normal and may experience abnormal bleeding.\(^14,15\) In most cases, carriers experience symptoms similar to...
those seen in men with mild hemophilia, as well as some that are specific to women. Symptomatic carriers and women with hemophilia may bruise more easily; may experience prolonged bleeding after surgery; may experience serious bleeding after trauma; often have heavier and more prolonged bleeding during their periods (menorrhagia) and are more likely to require an iron supplement or to undergo hysterectomy; and are more likely to have postpartum bleeding following childbirth.\(^{14,15}\)

### CLINICAL MANIFESTATIONS

Hemorrhage in patients with hemophilia may occur with minimal or unknown trauma. Patients with severe hemophilia (factor level of < 1 IU/dL or < 1% of normal) often experience spontaneous bleeding into joints or muscles. Those with moderate hemophilia (factor level of 1–5 IU/dL or 1%–5% of normal) seldom experience spontaneous hemorrhage and usually have prolonged bleeding with minor trauma or surgery. Patients with mild hemophilia (factor level > 5 IU/dL but less than 40 IU/dL or > 5% but < 40% of normal) experience severe hemorrhage only following moderate to severe trauma or surgery, and rarely experience spontaneous bleeding. Depending on the site, bleeding can be serious (joints; muscles, especially deep compartments [iliopsoas, calf, and forearm]; mucous membranes in the mouth, gums, nose, and genitourinary tract) or life-threatening (intracranial, neck/throat, gastrointestinal). The joints and muscles are the most common sites of bleeding (Table 1).

### MUSCULOSKELETAL BLEEDING

The hallmark of hemophilia is deep bleeding into the joints and muscles. Without prophylactic factor treatment, patients with severe hemophilia A or B may have a bleeding episode as often as once or twice a week. Hemarthrosis episodes typically begin when the child reaches the toddler age. One of the first signs of hemarthrosis is a tingling sensation and feeling of warmth which is soon followed by pain and decreased range of motion of the joint as a result of distension of the joint capsule. Prompt, aggressive treatment with factor replacement therapy is the key to prevent further bleeding and minimize potential long-term complications. Severe chronic arthropathy may develop in older children and adults who have not received aggressive treatment (Figure).

Bleeding into the muscle can manifest as a vague feeling of pain on motion. Swelling may not be obvious and the mass may be difficult to palpate, although the circumference of the affected limb will be increased. Among the muscle bleeds, iliopsoas bleed deserves a special mention because of its potential to cause life-threatening hypovolemic shock as large volumes of blood can be lost into the retroperitoneal space. These patients present with vague abdominal pain or upper thigh discomfort. The hip is flexed and outwardly rotated. The diagnosis is confirmed by computed tomography (CT) or ultrasound.

### LIFE-THREATENING HEMORRHAGE

#### Central Nervous System Bleeding

Most central nervous system (CNS) events, which involve bleeding inside the skull or spinal canal, are caused by trauma. CNS hemorrhage is the most common form of severe hemophilic trauma. However, since patients with hemophilia can experience bleeding even weeks

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**Table 1. Sites of Bleeding in Hemophilia**

<table>
<thead>
<tr>
<th>Site</th>
<th>Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joints (hemarthrosis)(^3)</td>
<td>70–80</td>
</tr>
<tr>
<td>Muscle</td>
<td>10–20</td>
</tr>
<tr>
<td>Other major bleeds</td>
<td>5–10</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

\(^3\) Occurs more frequently in hinged joints (eg, ankles, knees, elbows) than in multi-axial joints (eg, shoulders, wrists, hips).

after a minor head injury, a history of head trauma may be hard to determine, particularly in children. Spontaneous CNS bleeding in individuals with hemophilia is rare except when there has been a recent antecedent CNS hemorrhage (ie, a recurrent bleed at a previously injured site) or when there is an associated anatomic lesion that predisposes to acute hemorrhage (eg, aneurysm or arteriovenous malformation). Data from the Universal Data Collection Project of the U.S. Centers for Disease Control and Prevention indicates that predisposing risk factors for intracranial hemorrhage include HIV infection, presence of inhibitory antibodies, and age younger than 5 years or older than 51 years.

Neonatal intracranial hemorrhage is most commonly due to birth trauma. Difficult vaginal deliveries (often requiring the application of forceps or vacuum extraction) are predisposing factors for intracranial hemorrhage in hemophilic newborns.

The site of intracranial CNS bleeding can be subdural, epidural, or intraparenchymal. Bleeding at any of these sites can cause rapidly deteriorating CNS brain function, associated brain swelling, and, in the most extreme circumstances, herniation of the brainstem and rapid death.

If the bleeding is stopped with rapid clotting factor replacement, adverse clinical effects can be avoided. However, with intraparenchymal hemorrhage, even small hemorrhages can induce permanent structural and/or neurologic sequelae (in particular, if the anatomic site of the bleed is essential for routine brain function).

Throat and Neck Hemorrhage

An acute neck injury or a retropharyngeal hemorrhage induced by dental or oral surgical instrumentation can lead to a dissecting facial plane hematoma. This in turn can sometimes lead to compression and acute airway compromise. Bleeding from these injuries that is compressing or compromising the airway may require a rapid clinical response. The time from the injury until the trachea is compressed may be long, sometimes many hours. However, once the compression is sufficient to cause difficulty breathing, there may be a short amount of time to stop the bleeding and prevent complete respiratory obstruction.

MUCOCUTANEOUS BLEEDING

One of the common manifestations of hemophilia is oral bleeding. Tooth extraction poses a
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specific problem, and bleeding following extraction can be the first symptom that leads to the diagnosis of hemophilia. Bleeding after circumcision may also suggest the diagnosis. In a study cohort looking at sites of initial bleeding episodes in babies with hemophilia diagnosed before the age of 2 years, bleeding from circumcision and other iatrogenic causes tended to be most common in the neonatal period. Circumcision bleeding events occurred more often in infants with no family history (43%) as compared to those born to known maternal carriers (9.2%) or to mothers with some other family history of hemophilia (14.3%).

Gastrointestinal (GI) bleeding occurs occasionally in hemophilia, and a wide spectrum of esophageal and GI bleeding may occur. A review of 41 episodes of GI bleeding in hemophilia patients who presented to an institution over 10 years implicated duodenal ulcer (22%), unknown site (22%), and gastritis (14%) as the most common sources.

Mallory-Weiss syndrome has also been cited as a cause for upper GI bleeding in hemophilia patients.

PRINCIPLES OF TREATMENT

Understanding the pathophysiology of hemophilia as well as the type and severity of hemophilia and the inhibitor status in an individual patient are paramount in the management of a patient with hemophilia. In the past, management mainly focused on the treatment of acute bleeding episodes (Table 2). With data showing the benefit of bleed prevention, the management of hemophilia now focuses on prophylaxis of bleeding episodes, which prevents chronic arthropathy and improves quality of life.

ACUTE BLEEDING EPISODES

Dosing of Factor VIII Products

Dosing for factor VIII concentrate is as follows: 1 IU of factor VIII concentrate per kg will increase the circulating factor VIII level by 2% (ie, patient weight in kg × 50 IU/kg = 100% correction). For example, a 30-kg patient requiring 100% correction of factor VIII needs an infusion of 1500 IU of factor VIII (30 kg × 50 IU/kg).

Dosing of Factor IX Products

Dosing for factor IX concentrate is as follows: 1 IU of factor IX concentrate per kg will increase the circulating factor IX level by 1% (ie, patient weight in kg × 100 IU/kg = 100% correction). For example, a 30-kg patient requiring 100% correction of factor IX needs an infusion of 3000 IU of factor IX (30 kg × 100 IU/kg). Higher doses (120 to 130 IU/kg) of the recombinant factor IX product BeneFIX (Pfizer) may be needed to reach the 100% circulating factor IX level.

ADJUVANT THERAPY

Desmopressin

Desmopressin is a synthetic vasopressin analogue that increases plasma factor VIII and von Willebrand factor (VWF) levels; it is used to prevent and treat bleeding episodes associated with dental and surgical procedures in patients with mild and moderate hemophilia A and von Willebrand disease. Desmopressin causes the release of VWF and factor VIII from storage in the Weibel–Palade bodies of the endothelial cells that line the blood vessels. Individual response to desmopressin varies, with factor VIII level increasing between 2 and 15 times baseline level in patients with mild or moderate hemophilia A. It is therefore recommended that patients undergo a therapeutic trial of desmopressin with laboratory measurement of response to factor VIII before it is used for treatment of bleeding episodes or as prophylactic therapy before dental and other surgical procedures. A similar response is generally seen in an individual patient with subsequent doses, and thus the factor VIII level attained after a trial dose can be used to predict the response to future therapy.

The recommended intravenous dosage of desmopressin is 0.3 μg/kg, administered in 25
to 50 mL of normal saline, over a period of 20 to 30 minutes. A concentrated form of desmopressin is available for intranasal administration to treat bleeding disorders. The appropriate dose of concentrated intranasal desmopressin is 150 μg (1 puff) for persons weighing less than 50 kg, and 300 μg (1 puff in each nostril) for persons weighing more than 50 kg.

### Antifibrinolytic Therapy

Antifibrinolytics (both epsilon-aminocaproic acid [EACA] and tranexamic acid) reversibly block the lysine binding sites of plasminogen, preventing its activation to plasmin and thus inhibiting the lysis of polymerized fibrin. EACA is also believed to stabilize the active form of thrombin activatable fibrinolysis inhibitor (TAFIa). It is believed that inactivation of TAFIa is due to conformational rearrangements in the TAFIa molecule; EACA has been shown to slow down spontaneous inactivation of TAFIa, thus curtailing fibrinolysis.

### Table 2. Treatment of Acute Hemorrhage

<table>
<thead>
<tr>
<th>Type of Hemorrhage</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemarthrosis</td>
<td>FVIII 50 IU/kg initially, 20 IU/kg the following day</td>
<td>FIX 80 IU/kg initially, 40 IU/kg the following day</td>
</tr>
<tr>
<td></td>
<td>Consider additional treatment every other day, depending on response</td>
<td>Consider additional treatment every other day, depending on response</td>
</tr>
<tr>
<td>Muscle or significant subcutaneous hematoma</td>
<td>FVIII 50 IU/kg initially</td>
<td>FIX 80 IU/kg initially</td>
</tr>
<tr>
<td></td>
<td>Consider FVIII 20 IU/kg every other day until well resolved</td>
<td>Consider FVIII 40 IU/kg every other day until well resolved</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Local measures: pressure, packing</td>
<td>Local measures: pressure, packing</td>
</tr>
<tr>
<td></td>
<td>Antifibrinolytic therapy: FVIII 20 IU/kg if local measures fail</td>
<td>Antifibrinolytic therapy: FIX 30 IU/kg if local measures fail</td>
</tr>
<tr>
<td>Mouth, tooth extraction</td>
<td>FVIII 20 IU/kg (40 IU/kg if molar extraction)</td>
<td>FIX 40 IU/kg (80 IU/kg if molar extraction)</td>
</tr>
<tr>
<td></td>
<td>Antifibrinolytic therapy</td>
<td>Antifibrinolytic therapy</td>
</tr>
<tr>
<td>Iliopsoas hemorrhage</td>
<td>FVIII 50 IU/kg initially, then 25 IU/kg every 12 hr until asymptomatic, and then 20 IU/kg every other day for a total of 10–14 days</td>
<td>FIX 80 IU/kg, then 20–40 IU/kg every 12–24 hr to maintain factor IX level &gt; 40 IU/dL until asymptomatic, and then 30 IU/kg every other day for a total of 10–14 days</td>
</tr>
<tr>
<td></td>
<td>Consider repeat radiologic assessment before discontinuing therapy</td>
<td>Consider repeat radiologic assessment before discontinuing therapy.</td>
</tr>
<tr>
<td>Major surgery, life-threatening hemorrhage (eg, central nervous system, gastrointestinal, airway)</td>
<td>FVIII 50–75 IU/kg initially, then initiate continuous infusion of 3 IU/kg/hr to maintain factor VIII level &gt; 100 IU/dL for 24 hr, and then give 2–3 IU/kg/hr for 5–7 days to maintain the level &gt; 50 IU/dL and an additional 5–7 days at a level &gt; 30 IU/dL (it is acceptable to use bolus dosing to maintain these levels)</td>
<td>FIX 80–100 IU/kg initially, then 20–40 IU/kg every 12–24 hr to maintain factor IX &gt; 40 IU/dL for 5–7 days, and then &gt; 30 IU/dL for 5–7 days</td>
</tr>
<tr>
<td></td>
<td>Monitor factor VIII levels</td>
<td>Monitor factor IX levels</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Supportive measures: bed rest, vigorous hydration, evaluate for stones or urinary tract infections</td>
<td>Supportive measures: bed rest, vigorous hydration, evaluate for stones or urinary tract infections</td>
</tr>
<tr>
<td></td>
<td>If hematuria persists beyond 1–2 days, administer FVIII 20 IU/kg</td>
<td>If hematuria persists beyond 1–2 days, administer FIX 30 IU/kg</td>
</tr>
<tr>
<td></td>
<td>If not controlled, administer prednisone 1–2 mg/kg/day for 5–7 days</td>
<td>If not controlled, administer prednisone (1–2 mg/kg/day) for 5–7 days</td>
</tr>
</tbody>
</table>

**FIX** = factor IX; **FVIII** = factor VIII.

recurrent bleeding from oral mucosal surfaces is dramatically reduced with the use of antifibrinolytic agents. These agents are typically contraindicated in patients with hematuria because they can cause a clot to form in the urinary bladder or ureters, leading to obstruction.

EACA is available in intravenous, oral tablet, and elixir formulations; the oral dose is 100 to 200 mg/kg initially (maximum dose, 10 g), followed by 50 to 100 mg/kg per dose every 6 hours (maximum dose, 5 g). Tranexamic acid is available in 650-mg capsules; the dose is 25 mg/kg every 6 to 8 hours. To treat spontaneous oral hemorrhage or to prevent bleeding from dental procedures in patients with hemophilia, either drug is usually begun in conjunction with desmopressin or factor replacement therapy immediately prior to the procedure and continued for up to 7 days or until mucosal healing is complete. Nonsteroidal anti-inflammatory drugs and aspirin affect platelet function and hence are contraindicated in affected individuals.

PROPHYLAXIS

Patients with mild to moderate hemophilia typically bleed only after trauma, although the trauma needed to induce bleeding may be more minor than that which would cause bleeding in a normal individual. They usually do not suffer from significant morbidities, whereas patients with severe hemophilia often have spontaneous severe muscle and joint bleeds and can develop early crippling hemophilic arthropathy. Hence, routine prophylaxis has now become the standard of care in the United States and other developed countries in the management of patients with severe hemophilia. Prophylactic replacement therapy with cryoprecipitate in boys with severe hemophilia was first used nearly 50 years ago in Sweden and the Netherlands, and was shown to reduce the number and the severity of bleeds. Moreover, it was observed that early prophylaxis was more effective in preventing arthropathy compared to starting later in life, and that radiologic joint damage could not be reversed by prophylaxis. Subsequently, primary prophylaxis, defined as the start of regular, continuous treatment before the age of 2 years or after the occurrence of first joint bleed, was recommended and eventually became the standard treatment; it is currently recommended by the World Health Organization/World Federation of Hemophilia (WFH).

The timing to begin prophylaxis is somewhat controversial, but many authors suggest starting prophylaxis before the first hemorrhosis occurs. Several studies have reported a wide variation in the age at first joint bleed, ranging from 0.2 to 5.8 years, with medians of 1.6 to 1.7 years. It has been suggested that arthropathy is best prevented if prophylaxis is started before the second or third joint bleed, but the benefits of starting before the occurrence of first bleed have not been established. The Swedish experience provides strong support for early prophylaxis. In an analysis of 121 patients with severe hemophilia, age at initiation of prophylaxis was an independent predictor of the development of arthropathy, but dose and interval of prophylaxis at the start of prophylactic treatment were not.

In the Italian ESPRIT study, it was shown that children randomly assigned to prophylaxis had significantly fewer total bleeding episodes and joint bleeding episodes compared with those assigned to episodic therapy. Eleven of 21 patients (52%) in the prophylaxis group had on average less than 1 hemarthrosis per year, whereas only 4 of 19 patients in the episodic therapy group (21%) had the same low frequency of bleeding (P < 0.05). In a study of long-term prophylaxis versus on-demand treatment comparing age-matched Danish and Russian patients, the median annual number of joint bleeds in patients on prophylaxis was 1, while patients managed with on-demand treatment experienced a median of 37 joint bleeds. Patients taking prophylaxis also had a statistically significantly better quality of life estimate (P < 0.001) and better functional independence. In another trial, prophylaxis
was initiated between the ages of 6 and 30 months based on a history of joint hemorrhage rather than age. Radiologic evidence of preserved joint architecture was found in 93% of participants in the prophylaxis group at 6 years of age. In this group, 18 of 32 (56%) children had 1 or 2 bleeds into one or more index joints before prophylaxis, and 17 (53%) had 1 to 5 hemorrhages into 1 or more index joints during prophylaxis. Prophylaxis was efficacious in decreasing bleeding and joint damage after up to 5 hemarthroses.42

**Optimal Prophylactic Regimen**

Although the benefits of prophylactic replacement therapy are firmly established, the optimal dose and frequency remain unclear. The half-life of clotting factor concentrates is short: about 8 hours for factor VIII in children, and about 12 hours for factor IX. As a result, prophylactic therapy is most effective when given frequently. The most common factor VIII concentrate dosing regimen for prophylaxis in hemophilia A is 25 to 40 IU/kg 3 times per week; for hemophilia B, a dose of 80 to 100 IU/kg is given twice weekly. This is aimed at a pre-infusion level > 1% to mimic the clinical phenotype of moderate hemophilia.

Recently, the US Food and Drug Administration (FDA) approved the first long-lasting antihemophilic factor (recombinant) Fc fusion protein for use in adults and children with hemophilia A. This medication contains the Fc region of human immunoglobulin G1 (IgG1), which binds to the neonatal Fc receptor (FcRn). FcRn is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by cycling them back into circulation and prolonging their plasma half-life. Dosing for routine prophylaxis is 50 IU/kg every 4 days; it may be adjusted based on patient response, with dosing in the range of 25 to 65 IU/kg at 3- to 5-day intervals. More frequent or higher doses up to 80 IU/kg may be required in children younger than 6 years.45

**Development of Inhibitors**

**Factor VIII Inhibitors**

Despite the success in the clinical management of hemophilia A, treated patients remain at risk for developing neutralizing antibodies that inhibit factor VIII activity. An inhibitor is a polyclonal high-affinity IgG that is directed against the factor VIII protein and renders exogenous factor ineffective. IgG4 antibodies are predominant and do not fix complement.

**Risk Factors**

The pathophysiology underlying the development of factor VIII inhibitors is a T-helper (Th)–cell dependent event that involves antigen-presenting cells and B lymphocytes; why only a fraction of patients experience this adverse effect of factor therapy is not known. Patients with mild/moderate hemophilia have a lower risk for inhibitor development than those with severe hemophilia A. The estimated prevalence of inhibitors ranges from 3% to 13% in mild to moderate disease,44–46 and up to 36% in severe hemophilia A.47,48 Usually the presence of an inhibitor in patients with mild/moderate hemophilia is suggested by a change in bleeding pattern: patients who previously used to bleed only after trauma or surgery suddenly start to experience severe spontaneous bleeding. This change in bleeding pattern is explained by cross-reactivity of the inhibitor with the mutated factor VIII of the patient, resulting in a residual factor level of < 0.01 IU/dL.49–51 Occasionally, there is no change in the residual factor VIII level but an inhibitor is detected in the Bethesda assay and/or there is lack of efficacy of factor VIII transfusions.51–53

**Genetic factors.** Data indicate that the risk of developing neutralizing antibodies is to a large extent determined by patient-related genetic factors.54,55 The immune response to factor VIII is similar in up to 80% of family members, significantly higher than expected compared with data from unrelated subjects. In a meta-analysis
of patients with severe hemophilia A, the inhibitor incidence was twice as high in African American patients as compared with white patients.\(^5^6\) One study showed that patients of Hispanic ancestry with severe hemophilia A have a higher prevalence of neutralizing inhibitors than non-Hispanic white patients.\(^5^7\)

**Type of causative mutation.** In severe hemophilia A, the risk of inhibitor formation is associated with the type of mutation. More disruptive mutations in the factor VIII gene, such as the intron 22 inversion, large gene deletions, and stop codons are associated with an approximately 35% risk of inhibitor formation, compared with only about 5% in those with missense mutation and small deletions.\(^5^8\) Persons with mutations involving large gene deletions, nonsense mutations, and intrachromosomal aberrations are usually at higher risk for the development of inhibitors than persons with missense mutations, small deletions/insertions, and splice site mutations.\(^5^9,6^0\) A relatively high risk is also encountered in patients with splicing errors and frame-shift mutations.\(^6^1\)

**Major histocompatibility complex.** The HLA class I alleles A3, B7, and C7, as well as the class II alleles DQA0102, DQB0602, and DR15 have all been associated with a slightly higher risk for inhibitor development in unrelated patients, whereas the HLA C2, DQA0103, DQB0603, and DR13 alleles might be protective.\(^6^2,6^3\)

**Immune-regulatory molecules.** In the Malmö International Brother Study, polymorphic sites in the genes coding for interleukin 10 (IL-10), tumor necrosis factor-\(\alpha\), and cytotoxic T lymphocyte–associated protein 4 were all associated with the risk of developing inhibitors.\(^6^4-6^6\) In this study, a 134 bp–long variant of a CAA microsatellite in the promoter region (IL-10.G) was identified in 26.8% of patients with hemophilia A. Thirty-two of these patients (72.7%) developed inhibitors as compared with 37.5% of those without the allele.\(^6^5\)

**Intensive exposure to factor VIII.** Inhibitors in mild/moderate hemophilia seem to occur more commonly later in life, and an episode of intensive treatment with factor VIII concentrate has been reported to precede detection in most reported cases. In the series reported by Hay et al,\(^6^7\) 16 out of 26 inhibitors were detected after such intensive replacement therapy, and no particular concentrate was implicated.

**INHIBITORS TO FACTOR IX**

Factor IX inhibitors are relatively uncommon, occurring in only 1% to 3% of persons with hemophilia B. This is in striking contrast to hemophilia A, where approximately 30% of patients develop inhibitors. The majority of patients with hemophilia B who develop inhibitors have severe hemophilia B.

**Risk Factors**

Certain mutations in the factor IX gene are associated with an increased incidence of inhibitor development. Large deletions and frame-shift mutations leading to the loss of coding information are much more likely to be associated with inhibitor development. Large deletions account for only 1% to 3% of all hemophilia B patients, but account for 50% of inhibitor patients.\(^6^8\) Patients with hemophilia B who develop inhibitors are at risk for developing anaphylactic reactions to factor IX–containing products. Anaphylaxis occurred more frequently in families with null mutations (large deletions, frame-shift mutations, or nonsense mutations) than in those with missense mutations.\(^6^9\) With hemophilia A, approximately 40% to 50% of black individuals develop inhibitors, but no such association has been found in hemophilia B. Individuals who develop an inhibitor to factor IX do so relatively early in life (within the first 4 to 5 years), after a median of 9 to 11 exposure days to any factor IX–containing products. Because of the severity of a potential anaphylactic reaction occurring early in life after very few exposures to factor IX, all infants and small children with severe hemophilia B should be closely followed over their first 10 infusions with...
any factor IX–containing products in a facility equipped to treat anaphylactic shock. A comparison of inhibitors in hemophilia A and B is shown in Table 3.

### TREATMENT OF ACUTE BLEEDS IN PATIENTS WITH FACTOR VIII INHIBITORS

The available therapeutic agents for treatment of acute hemorrhage in children with hemophilia A with an inhibitor include high-dose recombinant or plasma-derived factor VIII concentrate, activated prothrombin complex concentrates (aPCCs), and recombinant activated factor VII (rFVIIa). In addition, antifibrinolytics may be used as an adjunct therapy.

Patient response to each treatment varies widely, with some patients responding well to one treatment and less well to another. Neither the patient’s history nor standard lab tests can assist in making the best choice for the patient. A personalized approach to factor selection is used, and the dosing of that particular agent is often determined primarily by clinical assessment. Inhibitors are quantitated using the Bethesda inhibitor assay and clinically are classified as low- and high-responding inhibitors (Table 4). Inhibitor screening should be done prior to invasive procedures and periodically during the first 50 days of treatment since the risk for inhibitor development is highest during this period.

### Low-Responding Inhibitors

A low-responding inhibitor is one in which inhibitor titers are \(< 5\) Bethesda units (BU)/mL; patients with low-responding inhibitors can generally be treated with factor VIII concentrates at higher doses. Because the effect of factor VIII inhibitor is usually delayed, the Bethesda titer in plasma is determined after a 2-hour incubation period. As a result of this time delay, continuous administration of factor VIII is usually found to be effective. For a serious limb- or life-threatening bleeding episode, a bolus infusion of 100 IU of factor VIII per kg of body weight is administered, and the level is maintained by treatment at a rate of 20 IU/kg/hr. An assay for factor VIII should be performed 1 hour after the bolus infusion and at least daily thereafter. As the antibody titer drops, the daily level of factor VIII may rise and thus downward adjustment of the continuous infusion rate may be required. For routine joint and muscle hemorrhage, patients can usually be managed with infusions at twice the usual dosage. Routine inhibitor assays should be performed after exposure to factor VIII to determine whether an anamnestic response has occurred.

### High-Responding Inhibitors

Most clinicians caring for patients with limb- or life-threatening bleeding episodes prefer to use

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**Table 3. Comparison of Inhibitors in Hemophilia A and B**

<table>
<thead>
<tr>
<th></th>
<th>Inhibitors in Factor VIII Deficiency</th>
<th>Inhibitors in Factor IX Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence of inhibitor development</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe disease</td>
<td>20%–30% of patients</td>
<td>Low incidence (2%–4% of patients)</td>
</tr>
<tr>
<td>Moderate to mild disease</td>
<td>3% to 13% of patients</td>
<td>Extremely rare</td>
</tr>
<tr>
<td><strong>Impact of race</strong></td>
<td>Increased incidence in people of African descent and Hispanics</td>
<td>No conclusive evidence of racial difference in incidence</td>
</tr>
<tr>
<td><strong>Frequency of infusion-associated reactions</strong></td>
<td>Rare</td>
<td>Occurs in (~60)% of patients with inhibitors</td>
</tr>
<tr>
<td><strong>Success of immune tolerance therapy</strong></td>
<td>60%–70% of patients</td>
<td>15%–30% of patients</td>
</tr>
<tr>
<td><strong>Complications of immune tolerance therapy</strong></td>
<td>Well tolerated</td>
<td>Nephrotic syndrome (especially in patients with a history of infusion reactions)</td>
</tr>
</tbody>
</table>

products for which therapeutic levels can be monitored. As described earlier, continuous administration of factor VIII is often effective because of the time delay in inhibition by the antibody. An initial dose of 100 to 200 IU/kg can be administered, and factor VIII levels can be determined 1 hour after initiation of continuous infusion at a rate of 20 to 40 IU/kg/hr. If a factor VIII level cannot be obtained (ie, patients with inhibitor titers > 5 to 10 BU/mL), alternative approaches include the bypassing agents aPCC and rFVIIa.

First used in the 1970s, aPCCs represented a significant improvement in the management in patients with hemophilia with inhibitors. They contain multiple activated serine protease molecules; activated factor X and prothrombin are the main active components in FEIBA (factor eight inhibitor bypassing activity), the most commonly used aPCC in the United States. FEIBA is a pooled plasma product that contains activated factors II, VII, IX and X, and has a duration of action of about 6 to 12 hours. For treatment of acute bleeds, the recommended dose of FEIBA is 50 to 100 IU/kg infused every 8 to 12 hours (maximum daily dose of 200 IU/kg). There is a risk of thrombosis/disseminated intravascular coagulation (DIC) with very large doses given frequently (> 200 IU/kg/day).

rFVIIa directly activates factor X and increases thrombin production on the surface of activated platelets in the absence of factor VIII or factor IX. Standard dosing of rFVIIa is 90 to 120 μg/kg, and many hemophilia treatment centers use higher doses (270 μg/kg/dose), especially in children and young adults. The half-life is about 1.5 to 3 hours, and therefore frequent administration (every 2–6 hours) is required. In one study that assessed the safety and efficacy of fixed-dose rFVIIa in the home setting, hemostasis was achieved in 566 (92%) of evaluable bleeding episodes, and following administration of the additional maintenance dose, hemostasis was maintained in 95% of successfully treated cases. As with aPCCs, there is no standardized quantitative laboratory test for measuring the effectiveness of rFVIIa therapy.

All currently used bypassing agents are associated with a risk of thrombotic complications including thromboembolism, DIC, and myocardial infarction. These complications are very rare in patients with hemophilia, however. In general, bypassing agents work for most bleeds and for most patients, but are not as predictable as factor replacement therapy and cannot be monitored by laboratory assays.

**TREATMENT OF ACUTE BLEEDS IN PATIENTS WITH FACTOR IX INHIBITORS**

rFVIIa and FEIBA are the mainstays of treatment of bleeding episodes in individuals with hemophilia B complicated by an inhibitor to factor IX. Treatment of hemorrhagic episodes in these patients depends on the type of bleeding episode experienced, the inhibitor classification (high- versus low-responding [Table 4]), and the history and severity of infusion reactions. Patients with low-responding inhibitors who have not experienced infusion reactions may be treated with doses of factor IX concentrate calculated to overcome the inhibitor titer and achieve a hemostatic level. In patients with high-responding inhibitors, the use of factor IX concentrates is impractical because of the inhibitor titer or the anamnestic response. Regardless of inhibitor titer, in

### Table 4. Characteristics of High- and Low-Responding Inhibitors

<table>
<thead>
<tr>
<th>High-responding inhibitors</th>
<th>Low-responding inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitor titers rise ≥ 5 BU/mL upon exposure to factor VIII or IX (anamnesis)</td>
<td>Inhibitor titers &lt; 5 BU/mL</td>
</tr>
<tr>
<td>Titers fall if no exposure</td>
<td>Do not rise with factor VIII exposure</td>
</tr>
<tr>
<td>No spontaneous remissions</td>
<td>Treat with large doses of factor VIII</td>
</tr>
<tr>
<td>Accounts for 60%–70% of inhibitors</td>
<td>May resolve spontaneously</td>
</tr>
</tbody>
</table>

BU = Bethesda unit.
patients with a history of an anaphylactic event, factor IX usage is contraindicated.

The most commonly used therapy for hemostatic control in patients with high-responding inhibitors with factor IX deficiency and a history of infusion reaction is rFVIIa; the standard dosing regimen is 90 to 120 μg/kg/dose administered every 2 to 3 hours, with a maximum dose of 270 μg/kg/dose. aPCCs, which contain factor IX, can be utilized if the patient has not experienced prior infusion reactions. Repeated exposures to products containing factor IX may stimulate the inhibitor titer and prevent its natural decline over time. This can pose a problem in cases of life- or limb-threatening hemorrhage unresponsive to rFVIIa as these patients will not have factor IX available as an effective mode of therapy. The dosing of FEIBA ranges from 50 to 100 IU/kg every 12 hours, with daily dosing not to exceed 200 IU/kg.

**IMMUNE TOLERANCE INDUCTION**

Because of the associated inhibitor-related morbidity resulting from limited treatment options, antibody eradication is the ultimate goal in inhibitor management. The only proven strategy for achieving antigen-specific tolerance to factor VIII or factor IX is immune tolerance induction (ITI) therapy. Successful ITI in hemophilia A is currently defined as both an undetectable inhibitor titer (< 0.6 BU), and normalized factor VIII pharmacokinetics, which in turn is defined as plasma factor VIII recovery > 66% of expected and a half-life > 6 hours, determined following a 72-hour factor VIII exposure-free period (Consensus Proceedings from the Second International Conference on Immune Tolerance Therapy, Bonn, Germany, 1997 [unpublished]). Once successful immune tolerance is achieved, long-term prophylaxis is commonly instituted. Using conclusions drawn from international consensus criteria and analysis of the International Immune Tolerance Registry, the I-ITI study has defined ITI failure by the presence of either of 2 criteria:

1. Failure to attain the definition of success within 33 months of uninterrupted ITI;
2. Failure to demonstrate a progressive 20% reduction in inhibitor titer over each 6-month period of uninterrupted ITI, beginning 3 months after initiation to allow for expected anamnesis.76–78

This definition implies a minimum ITI trial period of 9 months before failure is declared.

The European Hemophilia Standardization Board (EHSB), the International Consensus Panel (ICP), and the United Kingdom Hemophilia Center Doctors’ Organization (UKHCDO) have agreed that it is preferable to initiate ITI at a titer of < 10 BU/mL, unless, per the ICP, the titer does not decline over a period of 1 to 2 years and/or inhibitor development is associated with severe or life-threatening bleeding. The ICP noted that for “poor-risk” ITI patients (defined by a historical titer of > 200 BU/mL and/or a pre-ITI inhibitor titer of > 10 BU/mL and/or an interval of > 5 years since inhibitor diagnosis), published efficacy data are limited to dosing regimens > 200 IU/kg/day. The groups all independently concluded that ITI has been successfully performed using recombinant and plasma-derived factor VIII replacement therapy (usually the product on which they developed the inhibitor), and that there are no data to support the superiority of any single product type.79–81 However, both EHSB and ICP have suggested that VWF-containing concentrates be considered for patients who fail ITI using high-purity factor VIII.79,80

The recommendations from US guidelines for ITI in patients with hemophilia A and inhibitors are listed in Table 5.82

**ARTHROPATHY**

Before the advent of factor products for the treatment of hemophilia, hemarthrosis was
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One of the leading causes of morbidity. Today, the routine use of prophylactic treatment has resulted in a significant improvement in the lifestyle, quality of life, and life expectancy of these patients. However, despite best efforts, some patients will have severe joint destruction as a result of repeated articular bleeding episodes during their early years. This leads to pain and significant functional disability, thus impairing the quality of life. The basic pathology behind hemophilic arthropathy is chronic synovitis.

It is common to observe a pattern of repeated bleeding (chronic hemarthrosis), especially in patients with severe hemophilia, that can lead to chronic synovitis, inflammatory arthritis, and progressive arthropathy. Therefore, the key to preventing hemophilic arthropathy is aggressive management of the initial hemarthrosis. This is generally accomplished with the use of clotting factor replacement, restorative physiotherapy, and close clinical follow-up. If chronic synovitis develops, synovectomy may be considered in order to slow the progression of the hemophilic arthropathy and to prevent the development of major articular surface erosions that can lead to end-stage arthropathy. Primary prophylaxis is discussed earlier and is the mainstay of prevention of chronic hemophilic arthropathy.

SYNOVECTOMY

The emergence of chronic hemophilic hemarthrosis is incited by a hypertrophic and highly vascular synovium. Removal of the synovium prevents further joint damage, and can be accomplished through surgical and nonsurgical procedures.

Surgical excision of the hypertrophic synovium can be performed through open or arthroscopic procedures. The open approach has largely been replaced by arthroscopic synovectomies. Regardless of the approach, these patients need prolonged hospitalization, extensive factor replacement, and exhaustive physiotherapy. Moreover, patients with inhibitors are usually not considered candidates for surgical synovectomy.

Chemical and radioactive agents injected intra-articularly can decrease the volume and activity of the synovial tissue. Due to the minimally invasive nature of these procedures, nonsurgical synovectomies are of special importance for hemophilic patients with inhibitors to clotting factors.

Chemical Synovectomy

Chemical synovectomies, using thiotepa, osmic acid, D-penicillamine and other agents, have been used in the distant past. Rifampicin, which is used an antibiotic, is now the most

Table 5. Recommendations for Immune Tolerance Induction in Patients with Hemophilia A and Inhibitors

<table>
<thead>
<tr>
<th>The following patients should receive immune tolerance induction (ITI):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with severe hemophilia A and persistent inhibitor titer &gt; 5 BU/mL (confirmed on ≥ 1 repeat measurement) with a peak historical inhibitor titer &lt; 200 BU/mL.</td>
</tr>
<tr>
<td>Children with severe hemophilia A and inhibitor titer &gt; 5 BU/mL (confirmed on ≥ 1 repeat measurement) with a peak historical inhibitor titer &gt; 200 BU/mL, regardless of poor-risk characteristics.</td>
</tr>
<tr>
<td>Adults with severe hemophilia A and inhibitor titer &gt; 5 BU/mL (confirmed on ≥ 1 repeat measurement), regardless of inhibitor duration, should be considered for ITI, particularly those with frequent bleeding or a poor response to bypass therapy.</td>
</tr>
</tbody>
</table>

\[ a \] Strong recommendation, high-quality evidence (randomized controlled trials without important limitations or overwhelming evidence from observational studies).

\[ b \] Weak recommendation, low quality or very low-quality evidence (observational studies or case series).

\[ c \] Strong recommendation, low-quality or very low-quality evidence (observational studies or case series).

commonly used chemical for the purpose of synovectomy, and the one that has shown better results in terms of decreasing hemarthrosis. Each one of the injections should be accompanied by prophylactic administration of clotting factor concentrate. Excellent results (no synovitis and restoration of previous function) have been reported in up to 83% of patients at an average of 2.4 years after the intra-articular injection of rifampicin. As the pathology of the joint becomes more severe, however, the number of injections required to achieve improvement increases. Younger patients and smaller joints benefit more from this procedure.

Radiation Synovectomy

Radiosynovectomy (RS) and radiosynoviorthesis are common terms used to describe the synovial ablation accomplished by intra-articular injection of radioisotopes. Isotopes of gold, yttrium, rhenium, and dysprosium have been used to perform radiation synovectomies in patients with hemophilia. Yttrium-90, a pure beta emitter with adequate particle size and depth penetration, has been used successfully for the treatment of hemophilic synovitis.

The local (growth plate and articular cartilage) and remote effects of radiation are a concern. There have been no reported cases of growth plate disturbance after radiosynovectomy, even after the use of beta emitters such as gold-198. Articular cartilage is highly resistant to radiation, and although damage is theoretically possible, none has been reported. Progressive degeneration of treated joints does occur, but the rate is slower than that expected without radiosynovectomy. The principal concern is the potential for late, radiation-induced neoplasia. However, the safety of intra-articular radioisotopes is supported by a long-term follow-up study of more than 5000 RS procedures performed for rheumatoid arthritis, which found no reported radiation-induced malignancies.

One review analyzed the safety of RS in pediatric patients with hemophilia to provide a risk-benefit assessment. During knee RS, patients receive a radiation dose of approximately 0.74 mSv, and during elbow and ankle RS, a dose of approximately 0.32 mSv. The radiation dose from natural sources is approximately 2 mSv per year and the recommended limit for patients (apart from natural sources) is 1 mSv per year. The lifetime cancer risk increases about 0.5% per 100 mSv per year. Considering the risks and benefits of RS, the authors recommend that clinicians consider this procedure in children with inhibitors or in patients without inhibitors when bleeding is recurrent and persistent despite aggressive factor replacement. External-beam radiation has been extensively studied and carries a small risk of osteosarcoma induction.

ACQUIRED INHIBITORS TO FACTOR VIII

Acquired hemophilia (AH) has an estimated prevalence of 1.48 cases per million per year, and a reported mortality between 9% and 22%. AH is uncommon in children younger than 16 years (prevalence estimated at 0.045/million/year), and may be under-diagnosed in persons older than age 85 (prevalence estimated at 14.7/million/year). In the largest published population series, 50% to 60% of diagnosed individuals were previously healthy with no identified underlying disease state. Underlying conditions consistently associated with AH include pregnancy, evolving or pre-existing autoimmune or malignant disorders, and rarely medications. Primary among the autoimmune disorders are collagen vascular disorders, including systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, multiple sclerosis, and autoimmune hemolytic anemia. Most antibodies are mixtures of polyclonal IgG1 and IgG4 immunoglobulins, with the IgG4 molecules mainly responsible for inhibiting clotting activity. The clinical picture of AH is characterized by acute onset of severe
bleeding in individuals who previously had no history of bleeding diathesis. Patients generally present with mucocutaneous bleeding (eg, epistaxis and gastrointestinal bleeding), as well as soft tissue bleeding (eg, extensive ecchymoses and hematomas).

The 2 major goals of treatment of AH are the immediate control of acute and chronic bleeding and the long-term suppression/eradication of the autoantibody inhibitor. For patients with an inhibitor titer < 5 BU/mL, administration of desmopressin and concentrates of human recombinant factor VIII may raise the factor VIII activity levels in plasma. If the inhibitor titer is > 5 BU/mL, or if bleeding persists despite infusions of factor VIII concentrates, then factor VIII bypassing agents, such as aPCCs or rFVIIa, are indicated. Local measures for treatment of mucosal hemorrhage, such as antifibrinolytic agents or topical fibrin glues, are helpful.

The primary aim in long-term management of AH is to eradicate the factor VIII autoantibodies so that further bleeding can be averted. Although in some clinical situations (postpartum women and drug-related AH) factor VIII antibodies may remit spontaneously, most published guidelines and algorithms recommend early initiation of eradication therapy. This is usually achieved through immunosuppressive medications or immunomodulation. Successful immunosuppression regimens in AH have most frequently used corticosteroids as the cornerstone, either as a single agent or in combination with cyclophosphamide. In a prospective randomized trial involving 31 participants treated with prednisone 1 mg/kg/day for 3 weeks, 32% achieved complete remission. In participants with antibody persistence after 3 weeks, switching to oral cyclophosphamide 2 mg/kg/day as second-line therapy appeared more effective than continuing prednisone (complete remission rate 50% versus 42%).

Other immunosuppressive medications have been employed for eradication of refractory autoantibody inhibitors, including azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, and sirolimus. Controlled studies have not been performed to confirm their comparative safety and efficacy in sufficiently large populations. Anti-CD20 antibody has been used to treat inhibitors in patients with both congenital and acquired hemophilia. Other less frequently used treatment options include administration of intravenous immunoglobulins (IVIG) in large doses. IVIG by itself rarely is able to induce a complete remission, but may be useful adjunctive therapy along with immunosuppressants, as part of an ITI regimen, or with extracorporeal plasmapheresis.

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