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Wolters Kluwer

Acute treatment of bleeding and surgery in hemophilia A and B

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All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Jan 2024.**
This topic last updated: **Feb 22, 2024.**

INTRODUCTION

Hemophilia A (factor VIII [factor 8] deficiency) and hemophilia B (factor IX [factor 9] deficiency) are X-linked clotting factor deficiencies associated with bleeding of variable severity, from life-threatening to clinically silent.

The availability of factor replacement products has dramatically improved care for individuals with these conditions. However, patients may present with acute bleeding symptoms that require rapid treatment, and planning is required for patients undergoing surgery or invasive procedures.

This topic discusses the treatment of bleeding and perioperative management for individuals with hemophilia A and B.

Our approach is consistent with the World Federation of Hemophilia (WFH) Guideline updated in 2020 (available at https://www1.wfh.org/publications/files/pdf-1863.pdf) [1].

Other aspects of hemophilia A and B diagnosis and management are discussed in separate topic reviews:

- **Diagnosis** – (see "Clinical manifestations and diagnosis of hemophilia")
- **Prophylaxis** – (see "Hemophilia A and B: Routine management including prophylaxis")

- **Pregnancy** – (see "Clinical manifestations and diagnosis of hemophilia", section on 'Obstetric considerations')
- **Inhibitor eradication** – (see "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication")
- **Genetics** – (see "Genetics of hemophilia A and B")

- **Acquired hemophilia A** – Acquired hemophilia A is an autoimmune disorder caused by autoantibodies to factor VIII, referred to as inhibitors. Management differs because factor VIII products may be inactivated by the inhibitor, and immunosuppression is often required. These interventions are presented separately. (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)", section on 'Management'.)

ACUTE THERAPY FOR BLEEDING

For acute bleeding in patients with hemophilia, the immediate goal is to raise the factor activity to a level sufficient for hemostasis. The targeted factor activity level depends on the location and severity of the bleeding, the expected half-life of the product administered, and the presence of an associated injury or occurrence in a target joint.

Data to support the desired factor levels for treating acute bleeding come from extensive clinical experience and observational studies [1-3]. Randomized trials comparing different target factor levels have not been conducted.

Serious, life-threatening bleeding and head trauma

Key points for management in the emergency department — Serious or life-threatening bleeding in a patient with hemophilia is a medical emergency that requires immediate assessment and treatment with replacement factor. Guidelines from the United Kingdom Haemophilia Centre Doctors Organization (UKHCDO) suggest that the maximum time between arrival to the hospital and clinical assessment should not exceed 15 minutes, and if treatment for bleeding is required, the maximum time to its delivery should not exceed 30 minutes [4,5].

These include:

- **Treat first** – For patients with potentially serious or life-threatening bleeding, it is important to initiate treatment **immediately**, even before the diagnostic assessment is completed. Stated another way: **treat first, evaluate second, plan further therapy after weighing all relevant issues**.

- **Identify serious bleeding** – Serious or life-threatening bleeding includes any of the following [6]:

  - Central nervous system
  - Eye
  - Hip
  - Muscle (eg, iliopsoas and/or with neurovascular compromise or potential for neurovascular complications)
  - Abdominal
  - Gastrointestinal
  - Airway (eg, throat or neck)
  - Any bleeding severe enough to result in anemia and potentially require red blood cell transfusion(s)
  - Any prolonged bleeding that is not adequately responding to home-based therapy
  - Any significant injuries such as motor vehicle accidents or falls from distances of several feet or more

  Other locations where compartment syndrome and neurovascular complications could occur include the hand/wrist and the anterior compartment of the lower leg.

  If there is doubt about the seriousness of bleeding, it is preferable to treat the patient as if the bleeding is serious ("if in doubt, treat" [2]).

- **Transport if needed** – If the facility is not equipped to provide factor or bypassing products or not capable of monitoring using timely and specific coagulation studies, the patient should be transported to a facility that can provide this level of care [7,8]. If possible, factor should be administered before or during transfer.

- **Which product to give**

  - **Give their own factor product if available** – If the patient has the appropriate replacement therapy at home (or with them, if traveling), the product may be administered before leaving or en route to the facility, as long as this does not result in delays. In life-threatening circumstances, emergency medical transport should be called, and the product should be administered as soon as possible, including en route if needed.

    For hemophilia A, emicizumab does not treat acute bleeding once it has occurred treatment; a factor product must be used.

- **If their own factor product is not available** – If the patient does not have their own factor with them, recombinant factor is preferred. Plasma-derived factor can be used if recombinant factor is not available. (See 'Factor dosing for severe bleeding (patients without inhibitors)' below.)

  - Give factor VIII for hemophilia A.
  - Give factor IX for hemophilia B.

  The importance of **urgently giving the factor infusion** outweighs considerations of the specific factor preparation ("give the appropriate product that is available rather than spending time trying to obtain a different product").

- **Patients with inhibitors** – Patients with high titer inhibitors (>5 Bethesda units at any time in their history, regardless of current titer) generally require a bypassing agent (recombinant activated factor VII [rFVIIa] or activated prothrombin complex concentrate [aPCC]). (See 'Inhibitors' below.)

- **Imaging** – Factor administration should not be delayed while awaiting imaging studies in a patient with a concerning injury or suspected central nervous system bleeding [9-11].

  All significant head injuries must be considered nontrivial unless proven otherwise by imaging (eg, with computed tomography [CT] or magnetic resonance imaging [MRI]); serial observation may not identify injury until damage is already done.

Factor dosing for severe bleeding (patients without inhibitors) — Administration of factor should not be delayed while awaiting imaging studies or other testing.

For severe bleeding, the factor activity level should be maintained **above 50 percent at all times.** An immediate dose of factor should be given to raise the peak factor level to 80 to 100 percent (table 1). (See 'Key points for management in the emergency department' above.)

- **Quick calculation for the first dose** – Dosing calculations should not be an obstacle to immediate treatment of life-threatening bleeding. A quick calculation is as follows:

  - **Hemophilia A** – Give factor VIII at **40 to 50 units/kg** to produce a factor VIII level of 80 to 100 percent.

    Factor VIII is required for people using emicizumab prophylaxis. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Emicizumab for hemophilia A'.)

For patients receiving efanesoctacog alfa (Altuviiio), which has a half-life of approximately 48 hours, additional factor should generally not be given if it has been <2 days since the patient's prophylaxis infusion. However, this does not supersede clinical judgment in special circumstances such as intracranial bleeding, in which additional doses may be administered as needed based on factor VIII activity. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Efanesoctocog alfa (factor VIII-VWF fusion)'.)

- **Hemophilia B** – Give factor IX at **100 to 140 units/kg** to produce a factor IX level of 80 to 100 percent. If there is sufficient time to do the dosing calculation, determine the dose based on the formula: Dose (units) = % correction x Vd x weight (kg), using the Vd listed in the table for the specific product.

Do not waste factor (administer excess rather than discarding).

- **Measure peak and trough factor activity** – The peak factor activity level should be checked approximately 5 to 15 minutes after the first dose of factor. If this was not done, measure a trough factor activity and obtain a peak after the second dose. (See 'Monitoring and dose calculation for subsequent doses' below.)

- **Calculation for subsequent doses**

  - **Timing of next dose** – Additional doses should be timed to occur when a factor activity level of approximately 50 percent is anticipated (or documented), equivalent to approximately one half-life of the infused product, so the patient's circulating factor level does not drop below 50 percent. These calculations are based on peak and trough factor levels.

    Anticipated trough levels are based on the product used and desired trough level, with is >50 percent for major bleeds.

    It is important to be familiar with the specific assay used and how to interpret results, especially for patients receiving emicizumab and Altuviiio.

    - **Hemophilia A** – For life-threatening bleeding, check the trough approximately four to six hours after the first dose of a standard half-life factor VIII product. The next dose is due approximately 8 to 12 hours after the first dose for a standard half-life product. Longer intervals apply for extended half-life products (10 to 20 hours for most products, approximately 48 hours for efanesoctacog alfa [Altuviiio], which should be given at a repeat dose of 30 to 50 international units every two to three

days as clinically warranted if this product is continued for bleed treatment). Details of specific products are summarized in the table (table 2) and discussed separately. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Factor VIII products for hemophilia A'.)

- **Hemophilia B** – For life-threatening bleeding, check the trough approximately 8 to 12 hours after the first dose of a standard half-life factor IX product. The next dose is due approximately 18 to 24 hours after the first dose for a standard half-life product. Longer intervals apply for extended half-life products (from 54 to 104 hours). Details of specific products are summarized in the table (table 3) and discussed separately. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Products for hemophilia B'.)

Another option is to give a dose of factor to raise the level to 80 to 100 percent, followed by continuous infusion to maintain a consistent hemostatic level. This should be discussed with the hematologist or hemophilia treatment center (HTC). The ability to monitor stat factor activity levels is of utmost importance in this clinical scenario. (See 'Continuous infusion' below.)

- **Subsequent dose calculation** – The volume of distribution varies between factor replacement products, and the accurate dose calculation should be used to avoid significant under- or over-dosing that can occur when the proper calculations are not made. Patient age can also affect the volume of distribution. Subsequent doses of factor product will generally require one-half the percent correction as the initial dose, provided the patient has a trough factor level of approximately 50 percent. (See 'Monitoring and dose calculation for subsequent doses' below.)

- **Testing factor activity levels** – Details, including caveats with factor activity testing, are discussed below. (See 'Monitoring and dose calculation for subsequent doses' below and 'Check the factor level' below.)

- **Duration of treatment** – (See 'Duration of treatment' below.)

Hemarthroses

Considerations for hemarthroses — Bleeding into a joint (hemarthrosis) is one of the most common manifestations of hemophilia. Joint bleeds are characterized by reduced range of motion associated with pain or other unusual sensation (eg, tingling that often precedes pain), palpable swelling or warmth, or other typical findings for that patient. Bleeding into hip joints is concerning due to the greater risk of increased intra-articular pressure and osteonecrosis of the

femoral head. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Joints and muscle'.)

Some patients develop a "target joint" in which repeated bleeding episodes and chronic inflammatory changes occur. Treatment of a bleeding episode in a target joint may require higher doses of factor and more prolonged therapy to resolve the bleeding. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Hemophilic arthropathy'.)

Major aspects of assessment and management of joint bleeding include [12]:

- **Prompt factor infusion** – Factor should be infused promptly at the first sign of joint bleeding (eg, at the onset of tingling, pain, or typical symptoms of joint bleeding rather than waiting for reduced range of motion or swelling). Dosing depends on the specific joint and whether it has become a target joint. (See 'Factor dosing for joint bleeds' below.)

- **Assessment of bleeding** – Arthrocentesis is not required to diagnose joint bleeding in patients with hemophilia. If used (eg, to evaluate for suspected infection), factor should be administered before the procedure. (See 'Arthrocentesis (typically not used)' below.)

- **Reduce inflammation, pain, and bleeding** – Additional interventions to reduce bleeding, pain, and inflammation include avoidance of weight bearing or use of the affected extremity, application of ice packs, immobilization, and/or splinting as recommended. Standard rest, ice compression, and elevation (RICE) protocols apply. (See "Musculoskeletal injury in children and skeletally immature adolescents: Overview of rehabilitation for nonoperative injuries", section on 'Inflammatory phase' and "Initial management of soft tissue musculoskeletal injuries", section on 'Initial interventions: Utility and evidence'.)

  Give analgesics as needed, generally avoiding agents with antiplatelet activity such as non-selective nonsteroidal antiinflammatory agents (NSAIDs). An NSAID may be used in some circumstances such as significant joint inflammation in a patient receiving factor replacement. Selective cyclooxygenase 2 (COX2) inhibitors may be used since they do not have significant anti-platelet activity. (See "Overview of COX-2 selective NSAIDs".)

- **Identify other contributing factors** – Clinical evaluation is used to distinguish an acute bleed from other conditions such as pain due to chronic arthropathy, acute fracture or sprain, or infection. In many cases, this assessment is based on the history and physical examination rather than radiography or ultrasound examinations.

  Both hip and iliopsoas bleeding should be treated as major bleeding episodes, as should bleeding in any area where impending compartment syndrome can develop, including

bleeding near the wrists and hands and the anterior compartment of the lower leg. It may be challenging to distinguish hemarthrosis of the hip from bleeding into the iliopsoas muscle. In general, hemarthrosis of the hip results in severe pain with hip motion, whereas iliopsoas bleeding primarily causes limited hip extension. Iliopsoas bleeding may also cause reduced sensation over the ipsilateral thigh due to compression of the sacral plexus root of the femoral nerve. Ultrasonography or other radiologic evaluation may be helpful in identifying hematoma in the iliopsoas region versus the hip joint. (See 'Muscle/soft tissue bleeding' below.)

- **Hospital admission versus home care** – A decision must be made regarding whether the patient is safe to be treated at home versus requiring treatment in the hospital. The majority of hemarthroses are managed at home. Indications for hospitalization include:

  - Hemarthrosis that may be life or limb-threatening, such as suspected bleeding into the hip or iliopsoas muscle
  - Initial delay in therapy, leading to a more severe bleed or a bleed requiring more aggressive initial therapy
  - Suspicion of an infection
  - Need for joint aspiration due to increased joint pressure or possible infection
  - Bleeding in an individual with an inhibitor that is not responding well at home
  - Features that would favor continuous factor infusion rather than intermittent dosing
  - Bleeding episodes that are not responding as expected at home
  - Associated pain that is not controlled with home oral analgesia
  - Inability to adhere to home instructions/bedrest for any reason, including children who cannot be non-weight bearing, adults with significant arthropathy, patients with inhibitors requiring very frequent dosing, and patients with mild disease who have not learned how to use factor infusions

- **Other medications and hemostatic products** – Acute management needs that may be addressed in patients whose bleeding does not rapidly respond to factor infusion and local measures at home include possible admission with use of continuous infusion, inhibitor testing to ensure an inhibitor has not developed, possible joint aspiration to remove blood and relieve pressure, other hemostatic therapies, and glucocorticoids.

  - Other hemostatic therapies for individuals with inhibitors or those whose bleeding is not controlled by factor infusion are presented below. (See 'Adjuvant therapies' below.)

  - If a target joint has undergone repeated hemorrhage, we often administer a short course of glucocorticoids as appropriate to reduce pain and swelling associated with

synovial inflammation (eg, prednisone for three to five days), if the patient does not have an active infection. A benefit from a short course of glucocorticoids was demonstrated in a pair of trials that randomly assigned 35 children with hemophilia and a joint bleed to receive prednisone (1 mg per pound of body weight per day [equivalent to approximately 0.45 mg/kg; maximum dose, 80 mg] for three days) or placebo along with factor replacement therapy [13]. Compared with controls, the children assigned to prednisone had similar outcomes but required less factor infusion.

- **Treatment duration** – It can be challenging to determine when acute bleeding into a joint has stopped. Patient report of bleeding is most commonly used, and ultrasound may be helpful as well. Most experts continue to treat with a course of therapy designed to allow bleed resolution and prevent rebleeding based upon patient circumstances and the presence of a target joint, injury, or inhibitor. The duration of therapy depends on the joint affected, the size of the hemarthrosis, and the ability to avoid weight bearing, which affects the pace of healing. Some experts treat for approximately three to four days after bleeding has stopped; fewer infusions may be needed for patients receiving prophylaxis with emicizumab or an extended half-life product. Questions about individual treatment plans should be directed to the local HTC.

- **Joint rehabilitation** – Following resolution of a joint bleed, it is important to initiate a rehabilitation program that involves gradual increased range of motion, weight bearing, and strength training. Attention to bone health (eg, adequate vitamin D and knowledge regarding the presence of osteopenia) is also indicated.

  Involvement of a physical therapist with expertise in hemophilia to design a rehabilitative program is helpful. After a joint bleed, hemostatic coverage with factor infusion is needed during physical therapy to allow full rehabilitation. Individuals who are not receiving routine prophylaxis should consider using prophylaxis, including limited short-term prophylaxis following recurrent target joint hemarthrosis, with factor administration for several weeks to months to reduce or prevent recurrent bleeding, or to use a more aggressive dosing schedule in individuals who are already receiving routine prophylaxis.

  Details of prophylaxis are discussed separately. (See "Chronic complications and age-related comorbidities in people with hemophilia", section on 'Arthropathy' and "Hemophilia A and B: Routine management including prophylaxis", section on 'Exercise and athletic participation' and "Hemophilia A and B: Routine management including prophylaxis", section on 'Prophylaxis to reduce bleeding episodes'.)

Factor dosing for joint bleeds — Factor should be administered at the earliest sign of bleeding, preferably within two hours of bleed identification. This should be performed at home whenever possible to avoid delays in infusion.

The desired factor activity level depends on the site of bleeding and whether the joint has become a target joint (table 1). Do not waste factor (administer excess rather than discarding).

- **More serious bleeding** – Higher factor levels (eg, 80 to 100 percent) are used for bleeding into the hip, iliopsoas, or target joint, or bleeding associated with injury. Initial dosing is as presented above. (See 'Factor dosing for severe bleeding (patients without inhibitors)' above.)

- **Other joints** – For early hemarthrosis in peripheral joints such as knees, elbows, or ankles, the factor activity level should be raised to at least 40 to 50 percent. The formula for initial dosing to achieve approximately 40 to 50 percent factor activity uses a percent correction of 50 percent.

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The need for additional doses and the duration of therapy are individualized according to the patient's symptoms, affected joint, concurrent issues (bleeding into the hip, iliopsoas muscle, or a target joint; or bleeding associated with injury), and initial response. (See 'Monitoring and dose calculation for subsequent doses' below.)

For some patients who can identify the early symptoms of a joint bleed and rapidly administer factor, a single dose of factor may be sufficient. However, some comprehensive treatment centers use more intensive therapy for hemarthroses for specific patients or all patients (eg, for hemophilia A, an initial factor VIII dose of 40 units/kg followed by additional doses of 20 units/kg at 24 and 72 hours after the first dose; for hemophilia B, an initial factor IX dose to provide a target level of 80 percent activity followed by additional doses to provide 40 percent activity, with the interval determined by the half-life of the factor IX product used) [14].

At the other extreme, some individuals may require several days of factor infusion to allow bleed resolution and reduce the risk of rebleeding for a severe bleed, a bleed into a target joint, or a bleed with concurrent injury. Hip joint or acetabular hemorrhages may result in increased intra-articular pressure and osteonecrosis (aseptic necrosis) of the femoral head [15]. Therapy

designed to sustain a factor level above a trough of 40 percent for at least three days should be given, along with enforced bed rest; often this is done in the hospital using continuous infusion.

Arthrocentesis (typically not used) — Arthrocentesis is not required to diagnose joint bleeding in patients with hemophilia. If arthrocentesis is deemed necessary (due to concern of a septic joint or to reduce pressure from accumulated blood) it should only be performed after factor has been administered to raise the factor level to 100 percent in conjunction with a comprehensive hemophilia treatment center.

> Arthrocentesis may be appropriate if there is neurovascular compromise, severe pain, or other evidence of increased joint pressure that has not improved with other treatment, or there is suspicion of an infection. If joint aspiration is performed, replacement therapy should be administered to raise the factor level to 100 percent before the procedure. Inhibitor patients require use of bypassing therapy and should be treated at a comprehensive hemophilia treatment center.

Use of point-of-care musculoskeletal ultrasound (POC-MSKUS) is expanding [16-18]. POC-MSKUS performed by trained operators or full-joint ultrasound performed by a radiologist) may be useful to distinguish an acute bleed from pain associated with chronic arthropathy. POC-MSKUS is also helpful in joint aspiration. (See 'Overview of surgical planning' below.)

Muscle/soft tissue bleeding — Muscle bleeding may present with aching, stiffness, pain, or swelling. In muscle groups such as the upper arm, forearm, wrist, volar hand, and anterior or posterior tibial compartment, soft tissue hemorrhage may result in a compartment syndrome with impingement on the neurovascular bundle. This may be associated with tingling, numbness, and in severe situations, loss of distal arterial pulses.

Therapy should be initiated as soon as possible (at the first sign of symptoms or immediately after injury or trauma). For severe muscle hematomas, a peak factor activity level of at least 50 percent is appropriate as a minimum, but usually higher peak levels are used for severe muscle bleeding.

- This requires treatment/factor replacement therapy for individuals with any degree of factor deficiency in hemophilia A and B. Dosing is as for joint bleeding above. (See 'Factor dosing for joint bleeds' above.)
- For individuals with mild hemophilia A, it may be possible to raise the factor VIII level using DDAVP [19]. (See 'DDAVP for mild hemophilia A' below.)

Severe muscle bleeds require more than one factor infusion. Surgical decompression is undertaken only if medical therapy fails to forestall progression, and in consultation with a comprehensive hemophilia treatment center. (See "Acute compartment syndrome of the extremities", section on 'Management'.)

Muscle bleeds can result in a significant drop in hemoglobin level, and the hemoglobin should be monitored until it is clear that bleeding has ceased.

Minor bleeding — Minor bleeding such as epistaxis or skin bleeding may be treated with local measures including ice, pressure, or elevation. Topical therapies including antifibrinolytic agents or other adjunctive local therapies may also be helpful. At times, episodes of epistaxis may be prolonged or may result in larger volume blood loss that will necessitate replacement therapy. (See 'Antifibrinolytic therapy for mucosal bleeding or surgery' below and 'Adjunctive local therapies' below.)

MONITORING AND DOSE CALCULATION FOR SUBSEQUENT DOSES

Check the factor level — The factor activity level (peak and trough) is checked using a specific factor assay rather than an activated partial thromboplastin time (aPTT). The specific assays are aPTT-based or chromogenic. It is important to become familiar with the method of testing at one's institution in order to interpret the results accurately.

A peak factor level is not required with every dose. Ideally it is obtained after the first dose, to assess factor recovery and ensure there is no inhibitor, but if not assessed initially it can be obtained with a subsequent infusion.

Initial dosing may result in lower-than-expected trough levels if there is ongoing bleeding, particularly after major surgery. For major life-threatening bleeding, factor VIII activity is checked two to four hours after initial dosing for standard half-life factor VIII and four to six hours after initial dosing of standard half-life factor IX. Slightly longer intervals before the first trough level may be used for minor bleeding. After initial dosing, monitoring may need to be tailored to the expected half-life of the product being used.

- **Hemophilia A**
  - For people with hemophilia A receiving factor VIII prophylaxis, factor VIII is measured using a standard aPTT-based factor VIII activity assay.
  - For people with hemophilia A receiving emicizumab prophylaxis, a standard aPTT-based assay for factor VIII activity **cannot be used** because it is falsely

normalized/elevated with emicizumab. Factor VIII activity must be monitored using a bovine substrate-based chromogenic assay [20]. (See 'Patients with hemophilia A receiving emicizumab' below.)

- For people with hemophilia A receiving efanesoctacog alfa (Altuviiio), a validated one stage clotting assay should be used to measure factor VIII activity. Other assays (chromogenic or aPTT-based) may overestimate factor VIII activity by approximately 2.5-fold. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Efanesoctocog alfa (factor VIII-VWF fusion)'.)

- **Hemophilia B**

  - For people with hemophilia B receiving factor IX prophylaxis, factor IX activity is measured using a standard aPTT-based factor IX activity assay.

Calculate the second and subsequent doses — While the initial dose is given rapidly for life-threatening bleeding, subsequent dosing is based on the peak and trough levels after the initial dose and the volume of distribution (Vd) of the specific factor product being administered. Significant over-dosing or under-dosing may occur if this calculation is not used or if the factor is given on a fixed schedule without monitoring. The second and subsequent doses will be approximately one-half of the initial dose when given after one half-life, provided the patient's trough factor level is approximately 50 percent.

However, individual pharmacokinetics can significantly impact factor half-life and ultimate hemostasis. The volume of distribution may vary by patient and can be affected by acute hemorrhage and body fat content [21].

The following calculation should be used to determine the appropriate factor dose:

Dose (units) = % correction x Vd x patient weight (kg)

For the % correction, use 100 for a desired factor activity of 100 percent. If the patient's trough level is 50 percent and the desired factor activity is 100 percent, then the percent correction is 50%.

For the Vd:

- **Factor VIII** – All products have a Vd of approximately 0.5 dL/kg.
- **Factor IX** – The Vd varies by product.

Sample calculations:

- **Hemophilia A** – For a 60 kg patient treated with a recombinant factor VIII product with Vd of 0.5 dL/kg who requires a factor level of 100 percent and has a trough value of 50 percent, the dose is calculated as follows:

  50 (% correction) x 0.5 (Vd) x 60 kg (weight) = 1500 international units of recombinant factor VIII concentrate.

- **Hemophilia B** – For an 80 kg patient treated with Benefix (Vd = 1.3 for age ≥12 years) who requires a factor IX level of 100 percent and has a trough value of 50 percent, the dose is calculated as follows:

  50 (% correction) x 1.3 (Vd) x 80 kg (weight) = 5200 international units of Benefix.

Do not waste factor (administer excess rather than discarding).

Subsequent doses are given at intervals of approximately one half-life of the infused product, which is modified based on peak and trough levels for that individual during that bleeding event. Approximate half-lives for specific products are listed in the table (table 3).

If the trough factor activity is lower than expected, the dosing interval may be shortened and/or the subsequent dose increased depending on peak levels. If the trough factor activity level is higher than expected, the dosing interval may be increased and/or the subsequent dose may be lowered.

Continuous infusion — Continuous infusion is another option for maintaining stable factor activity levels [22-27]. This offers the advantages of consistent factor levels, less-frequent monitoring, and decreased factor use over time.

- **Factor VIII** – A dose of approximately 4 international units/kg/hour of standard half-life factor VIII concentrate will often maintain the level initially achieved by the bolus infusion.

- **Factor IX** – A dose of approximately 6 units/kg/hour of standard half-life factor IX concentrate will often maintain the level initially achieved by the bolus infusion.

- **Longer half-life products** – Longer half-life products have been used in continuous infusion, but lower doses and closer monitoring of levels are recommended.

Factor activity levels should be checked periodically during continuous infusion, with the interval determined by the previous level, dose adjustments, and clinical bleeding. Continuous infusions should not have an attached filter, and the factor product should only be mixed with normal saline.

Duration of treatment — The duration of high dose factor administration is individualized based on the site of bleeding, severity, need for surgery, and assurance that bleeding has stopped.

- **Head trauma** – We often treat for at least three days, including significant trauma with negative imaging.
- **Documented intracerebral hemorrhage (ICH)** – Prolonged therapy (eg, for three weeks) is generally required, followed by a period of prophylaxis or initiation of long-term prophylaxis, as the risk of recurrent ICH is often increased.
- **Joint or muscle** – Patients who require physical therapy or rehabilitation may need to use prophylactic dosing until the patient is fully recovered. Dosing relative to physical therapy should be timed so that physical therapy can occur when the factor level is high, not during the trough.

  Late bleeding following head trauma can occur up to three to four weeks following the event. Individuals with head trauma or other severe bleeding should be instructed about signs of late or recurrent bleeding, plans for factor dosing should these occur, and parameters for seeking medical attention, so that treatment can begin at the earliest manifestation of recurrent bleeding.

URGENT/EMERGENCY SURGERY

Patients who require an emergency procedure should be managed with urgent infusion of factor to raise the factor activity to a level appropriate for the procedure. (See 'Major surgery' below and 'Elective surgery' below.)

ELECTIVE SURGERY

Overview of surgical planning — Planning for elective surgery should include the patient, family/caregivers, and all relevant clinicians to ensure that best practices are followed. Collaboration with experts from a hemophilia treatment center to develop a hemostatic, effective, and safe care plan is strongly advised. A comprehensive plan for management before, during, and after the procedure, and excellent communication between the operating physician, anesthesiologist, patient, family/caregivers, pharmacy or other location where the product is stored, and the hematologist is required to assure an optimal outcome [28]. (See

"Hemophilia A and B: Routine management including prophylaxis", section on 'Hemophilia treatment centers'.)

Surgery should be performed in a setting that includes timely access to laboratory monitoring of factor activity levels and immediate availability of replacement factor (or plasma components, in resource-limited settings) and other hemostatic products, and clinicians with expertise in managing patients with hemophilia. Meticulous operative technique should be used, with local hemostatic agents as appropriate.

The preoperative assessment should include:

- General medical examination to identify associated issues including oral health prior to joint replacement, other hemostatic defects (eg, concomitant liver disease), use of medications that can affect the coagulation system (including over-the-counter and herbal medications), and/or cardiovascular risk factors or cardiovascular disease.

- Inhibitor screening to identify newly developed inhibitors and/or determine the inhibitor titer. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication", section on 'Routine screening and preoperative testing'.)

- Consideration of issues related to monitoring of factor replacement (eg, rapid turnaround time for factor assays). Availability of specific monitoring tests should be confirmed, including appropriate bovine substrate-based chromogenic assays for individuals receiving emicizumab as well as a validated one-stage clotting assay to evaluate factor VIII activity in patients receiving efanesoctacog alfa (Altuviiio). (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Emicizumab for hemophilia A' and "Hemophilia A and B: Routine management including prophylaxis", section on 'Efanesoctocog alfa (factor VIII-VWF fusion)'.)

- DDAVP (1-deamino, 8-D arginine-vasopressin, also called desmopressin) test dose for individuals with mild hemophilia A for whom this approach is being considered and has not been performed already; this should be done at least one week before planned surgery. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'DDAVP test dose for mild hemophilia A'.)

Desired factor levels and duration of therapy depend on the type of procedure, as described below, with longer durations for greater bleeding risk procedures or procedures where healing requires a longer duration of coverage. DDAVP may be used in patients with mild hemophilia A who have been demonstrated to have an adequate response and in appropriate procedures (eg, dental procedures). Antifibrinolytics are often useful in dental procedures or other

interventions affecting mucosal surfaces. (See 'Major surgery' below and 'Circumcision' below and 'Dental procedures' below and 'Endoscopy' below and 'Adjuvant therapies' below.)

For patients who require perioperative factor administration, the initial (preoperative) dose should be timed to provide maximal coverage at the time of greatest bleeding risk (typically 30 to 60 minutes before the procedure). The dose is calculated from the patient's weight, baseline factor level, desired factor level, volume of distribution, and presence of an inhibitor as described in the dosing sections above. For the first dose, we assume the baseline factor level to be 0 percent. It is generally not necessary to subtract the patient's baseline factor activity level.

After infusion, an immediate (stat) factor level should be checked before proceeding with the operative intervention for all procedures other than routine outpatient dental procedures. In a patient who has been receiving emicizumab, a bovine substrate-based chromogenic factor VIII assay must be used. In a patient with an inhibitor who is using bypassing therapy, there is no coagulation test that reflects clinical efficacy; therefore, laboratory monitoring of factor activity levels is not used.

Subsequent dosing is based on the plan of care developed, the patient's clinical status, and the measured levels, which, if bolus dosing is used, are typically measured at 8 to 12 hours after the previous dose for factor VIII and 12 to 24 hours after the previous dose for factor IX [29,30]. In addition, levels are often obtained in the recovery room to assure adequate hemostasis.

If there is unexpected intraoperative and/or postoperative bleeding, it is important to obtain an immediate (stat) factor level and, as long as not using a bypassing agent, to consider the possibility that bleeding may be due to an anatomic or mechanical cause (eg, need for ligation of blood vessels) if adequate hemostatic factor levels are documented.

The efficacy and safety of extended half-life factor VIII products (recombinant factor VIII-Fc fusion; PEGylated recombinant factor VIII) has been demonstrated in small studies in which patients with hemophilia A were managed perioperatively for major and minor surgeries and had excellent hemostasis without serious adverse events [31,32]. Wider clinical experience has accumulated since the licensure of these products, and experience supports the safety and efficacy seen in earlier studies. Product consistency during outpatient and inpatient use is a consideration, and if the patient uses a longer-lasting product or specific product at home, we use the same product in the hospital if possible. (See 'Breakthrough bleeding during prophylaxis with a longer-lasting factor' below.)

Patients with mild hemophilia A and those who have received intensive factor replacement for the first time should be re-screened for inhibitors at the completion of therapy, and at

approximately two to three weeks postoperatively [2]. Patients for whom factor administration is ineffective and those requiring higher than expected doses of factor may also require earlier inhibitor screening. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication", section on 'Screening and early diagnosis'.)

Major surgery — Major surgery includes any surgery with a risk of clinically significant bleeding or penetration of a major body cavity, including orthopedic surgery. Decisions regarding major surgery are best made in close consultation with the patient and an experienced multidisciplinary team including a comprehensive hemophilia treatment center hematologist (to confirm that factor replacement and other hemostatic therapies are optimally administered) and the surgeon (to assess the feasibility of the procedure and likelihood of efficacy) [3].

For the management of major surgery in which postoperative continuous infusion is planned, the infusion is often started before the surgery, after the initial bolus is administered. Factor VIII and factor IX clearance (consumption) is increased during surgery due to expected intraoperative blood loss. A follow-up bolus may be needed before initiating the continuous infusion. This is especially pertinent to orthopedic procedures.

Orthopedic procedures are the most commonly performed major surgical procedures in people with hemophilia. Joint surgery may be indicated in some cases of chronic synovitis or arthropathy. Various procedures may be offered, including:

- Synovectomy, either isotopic or surgical, for recurrent bleeding
- Joint replacement or joint fusion for extensive joint damage

A 2016 meta-analysis of studies evaluating the role of total knee arthroplasty (TKA) in people with hemophilia reviewed outcomes of 336 procedures in 254 individuals and found an overall improvement in range of motion, although not as great as that of individuals without hemophilia [33]. The complication rate was 32 percent; common complications included infections, bleeding, and bone abnormalities. This emphasizes the importance of bone health and maintaining optimal bone density.

Individuals with hemophilia can undergo any type of major surgery (eg, cancer surgery, coronary artery bypass grafting [CABG]) as long as factor replacement is given and adequate hemostasis ensured. (See "Chronic complications and age-related comorbidities in people with hemophilia", section on 'Cancer' and "Chronic complications and age-related comorbidities in people with hemophilia", section on 'Cardiovascular disease'.)

The target factor activity level and duration of therapy are individualized according to the patient and procedure. Most recommendations, including the 2020 World Federation of

Hemophilia guideline, use a desired preoperative factor level for major surgery of 80 to 100 percent for hemophilia A and 60 to 80 percent for hemophilia B, with postoperative levels gradually tapering to approximately 50 percent until the wound is healed (typically over a period of 10 to 14 days) [1]. For wound or joint manipulation, a level of at least 50 percent is necessary.

Dosing to achieve the appropriate factor level, including calculations for bolus dosing or continuous infusion, which may provide more consistent factor levels and reduce factor usage, is described above. (See 'Acute therapy for bleeding' above.)

Circumcision — Circumcision is an important decision for some families/caregivers and is of religious significance for certain populations such as Muslims. Circumcision in the neonatal period is often the first hemostatic challenge in an individual with hemophilia, and in some cases the first clue to the diagnosis. All individuals for whom the diagnosis of hemophilia is possible based on family history should have factor activity testing with results obtained and discussed with a hemophilia treatment center hematologist before a circumcision is performed. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Neonatal diagnosis'.)

If the diagnosis of hemophilia is confirmed and the family/caregivers request circumcision, the following is advised:

- The use of preoperative factor is individualized. At our center, we generally do not administer factor prior to the procedure if circumcision is performed via a method such as the Plastibell device because bleeding is generally not excessive. However, we ensure that replacement factor is available at the time of the procedure should it be needed.

  If anesthesia is needed before a penile block, factor may be administered beforehand.

  If circumcision is performed via a method such as a the Gomco clamp, then one dose of replacement therapy (the smallest vial size available) is administered prior to the procedure; in addition, local hemostatic therapies may be used and the family/caregiver is educated to assure the wound is not disrupted. (See "Neonatal circumcision: Techniques", section on 'Techniques'.)

- Observation post-procedure is likely to require a longer period than used for neonates without hemophilia. If postoperative bleeding occurs, further or initial replacement therapy is required as well as use of local hemostatic agents. Prolonged bleeding may require additional doses.

- Fibrin glue (also called fibrin sealant) comes as a kit made from plasma-derived clotting proteins that is applied to the external surface of a wound as a spray or patch. The products contain concentrated fibrinogen (the precursor of fibrin) and coagulation factor XIII, which crosslinks fibrin. Fibrin sealant can be used for those with hemophilia with bleeding that cannot be controlled with local measures. This product lessens the need for factor replacement and is not associated with some of the risks and expense of factor administration [34]. Specific products and their uses are discussed in more detail separately. (See "Fibrin sealants".)

  Gelatin granules and other topical agents can also be used. (See "Overview of topical hemostatic agents and tissue adhesives", section on 'Gelatin matrix' and "Overview of topical hemostatic agents and tissue adhesives", section on 'Topical thrombin'.)

- Antifibrinolytic agents such as tranexamic acid or epsilon aminocaproic acid reduce bleeding by interfering with fibrinolysis and thus reducing clot breakdown; they can be used orally or intravenously. In our experience, these agents are less effective as a single agent in circumcision. (See 'Antifibrinolytic therapy for mucosal bleeding or surgery' below.)

- The procedure should be performed so that the risk of bleeding is minimized (eg, experienced hands, use of Plastibell device if available). This and other techniques are discussed separately. (See "Neonatal circumcision: Techniques", section on 'Techniques'.)

For the most part, practice is based on clinical experience rather than evidence from randomized trials. The variation in practice among experts is illustrated in the following:

- A 2015 survey of pediatric hematologists affiliated with hemophilia treatment centers (HTCs) in the United States documented a wide range of approaches among 64 respondents and lack of established protocols in most cases [35].

  - **All respondents** stated they would use at least one dose of factor before the procedure; approximately one-third used two or three doses; and an additional 12 (19 percent) used more prolonged therapy.

  - Major concerns included the risks of bleeding and inhibitor development after early exposure to replacement product.

  - Two respondents (3 percent) would not allow the procedure unless there was a urologic indication, 18 (28 percent) would perform the procedure at the time of another

procedure that required factor administration, and 20 (31 percent) would defer the procedure until the child was older.

- The remaining 24 (38 percent) would perform the procedure (some reluctantly).
- Most used a target factor level of approximately 75 percent; often a level of 100 percent or higher is used because the smallest vial size provides this level for a small infant, and the entire vial is given so as not to waste the product.
- Approximately one-third used antifibrinolytic therapy, and smaller numbers used fibrin glue, topical thrombin, gelatin sponge, or wound seal.

- A 2009 review and survey conducted by the European Haemophilia Therapy Standardization Board (EHTSB) identified six studies involving 163 patients with hemophilia who underwent circumcision [36]. Five of the studies used factor replacement plus local therapy (fibrin glue, antifibrinolytic agents) and one used antifibrinolytic agents alone. Target factor levels when reported were in the range of 30 to 60 percent. The survey of experts suggested a target factor activity level of 80 percent for three to four days, with adjunctive fibrin glue and/or antifibrinolytic therapy.

Additional information about risks and benefits of circumcision, methods for analgesia, and complications are presented separately. (See "Neonatal circumcision: Risks and benefits" and "Neonatal circumcision: Techniques" and "Complications of circumcision".)

Tonsillectomy — Tonsillectomy is a high-risk procedure in individuals with hemophilia. In particular, the risk of bleeding from tonsillectomy may be especially concerning because the bleeding may be not only oral but also retropharyngeal; the latter may be associated with airway compromise. Delayed bleeding is a significant risk and can lead to hypotension and shock. Due to the location of potential bleeding, attention to hemostasis is especially important.

- **Factor replacement** – Factor replacement is used for those with severe or moderate, and often mild hemophilia, typically for a prolonged period of at least several days or longer (14 days is common), since the risk of bleeding continues until the eschar falls off.

  Dosing to achieve the appropriate factor level, including calculations for bolus dosing or continuous infusion, which may provide more consistent factor levels and reduce factor usage, is described above. (See 'Acute therapy for bleeding' above.)

- **Antifibrinolytic agent** – An antifibrinolytic agent is always used. The duration may continue until the eschar falls off, which can occur at day 12 or even later.

Dental procedures — Different dental procedures are associated with different bleeding risks. Close consultation between the dentist and hemophilia treatment center prior to the procedure is advised. A summary of recommendations from the United Kingdom Haemophilia Center Doctors' Organization (UKHCDO) in 2013 included the following recommendations, largely based on low quality evidence [37]:

- **Indications for factor administration**
  - **Inferior dental block** – For children and adults with hemophilia undergoing inferior dental blocks, factor replacement to a level of 50 percent activity during the procedure is required. The dose of factor should be administered as close to the procedure as possible.
  - **Impacted wisdom teeth** – Serious risks are associated with extraction of impacted mandibular third molars (wisdom teeth), due to the potential for retropharyngeal bleeding and airway compromise.
  - **Local anesthesia**
    - **Children, moderate to severe hemophilia** – For children with moderate to severe hemophilia, factor levels may rarely need to be raised for local anesthetic infiltration.
    - **Adults, moderate to severe hemophilia** – For adults with moderate to severe hemophilia, certain dental procedures may not require factor infusion; examples include buccal infiltration, inter-papillary injection, endodontic (root canal) treatment, and intra-ligamentary injections. However, we do have patients infuse factor for lower posterior root canals. For adults undergoing dental extractions, the use of sutures and topical hemostatic gelatin matrices or cyanoacrylate tissue adhesives may minimize bleeding. (See "Overview of topical hemostatic agents and tissue adhesives", section on 'Gelatin matrix' and "Minor wound repair with tissue adhesives (cyanoacrylates)".)
- **Target factor level** – For children and adults with hemophilia undergoing dental procedures that require factor replacement, a target factor level above 50 percent for one to two days is usually sufficient. This often can generally be achieved with one infusion of factor plus antifibrinolytic therapy. Factor infusions should be scheduled in such a way that the number of infusions is minimized. Dosing to achieve the appropriate factor level is described above. (See 'Acute therapy for bleeding' above.)

- **Mild hemophilia** – For children and adults with mild hemophilia (factor activity level above 5 percent), the majority of non-surgical dental procedures can be provided by the pediatric and adult dentists without additional interventions. Exceptions include block injections as noted above. Periodontitis and gingival inflammation increase the risk of bleeding.

- **Antifibrinolytic therapy** – Antifibrinolytic agents (eg, tranexamic acid, epsilon aminocaproic acid) are very useful for oral procedures because fibrinolysis is highly active on mucosal surfaces. These can be given orally, intravenously, or as a mouthwash; the mouthwash should be restricted to older children and adults because it may be inadvertently swallowed by younger children (see 'Antifibrinolytic therapy for mucosal bleeding or surgery' below). Antifibrinolytic agents can also be safely combined with factor replacement; care should be taken when co-administered with FEIBA [38]. A typical regimen is to give the first dose of the antifibrinolytic agent two hours before the procedure and continue for up to 7 to 10 days post-procedure.

Endoscopy — Due to the location of potential bleeding, attention to hemostasis is especially important.

- **Moderate to severe hemophilia** – Factor replacement is used for individuals with moderate to severe hemophilia A or B undergoing endoscopy. More than one infusion of factor may be required.

- **Mild hemophilia**

  - For mild hemophilia A, DDAVP may be sufficient based on the patient's factor level and response; response to DDAVP needs to be documented before this approach is used. (See "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care", section on 'DDAVP trial'.)

  - For mild hemophilia B, factor replacement is used.

  Dosing to achieve the appropriate factor level, including calculations for bolus dosing or continuous infusion, which may provide more consistent factor levels and reduce factor usage, is described above. (See 'Acute therapy for bleeding' above.)

- **Antifibrinolytic therapy** – If biopsies are taken, postprocedural antifibrinolytic therapy should be considered. (See "Gastrointestinal endoscopy in patients with disorders of hemostasis".)

SPECIAL POPULATIONS

Patients with hemophilia A receiving emicizumab — Individuals with hemophilia A who are receiving emicizumab, a bispecific monoclonal antibody (mAb) that substitutes for the function of factor VIII in hemostasis (figure 1), have a number of considerations related to treatment of bleeding or surgery. Emicizumab half-life is very long; the mAb remains in the patient for as long as six months after discontinuation. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Emicizumab for hemophilia A'.)

A hemophilia treatment center should be consulted to ensure that these are taken into account when determining the treatment plan.

- **Patients without inhibitors** – Emicizumab is not used for acute bleeding; factor VIII replacement is required. For individuals receiving emicizumab who do not have a factor VIII inhibitor, factor dosing is similar to other hemophilia A patients without inhibitors, with the caveat that measurement of factor VIII activity requires a bovine substrate-based factor VIII assay. For those who require factor infusions, the calculations for dosing generally assume that the patient is at their baseline level (ie, calculations should be the same as for any other patients). Consultation with a hemophilia expert or the local hemophilia treatment center is advised. (See 'Acute therapy for bleeding' above and 'Check the factor level' above.)

  Reports describing surgery in individuals with hemophilia A receiving emicizumab who require surgery have documented that minor surgery may not require factor replacement and major surgery or minor surgery with persistent bleeding may be effectively treated with factor VIII [39,40].

- **Need for bovine substrate-based factor VIII activity assay** – Emicizumab interferes with the assay for factor VIII activity based on the activated partial thromboplastin time (aPTT). A standard aPTT-based assay for factor VIII activity **cannot be used** because it is falsely normalized/elevated by emicizumab. A bovine substrate-based chromogenic assay for factor VIII activity must be used [20].

- **Inhibitor patients** – Emicizumab is not used for acute bleeding; patients with high responding factor VIII inhibitors require a bypassing agent to treat clinically relevant bleeding, and for patients on emicizumab, rFVIIa is recommended. For patients receiving a bypassing agent, dosing considerations need to be followed to avoid the potential risk of thrombotic microangiopathy (TMA). Recombinant activated factor VII (rFVIIa) is the recommended first-line treatment for breakthrough bleeding in patients with hemophilia A with high responding or high titer inhibitors who are receiving emicizumab. (See 'High titer or high responding inhibitor - Use a bypassing product (rFVIIa or FEIBA)' below.)

- TMA has occurred when the activated prothrombin complex concentrate (aPCC) FEIBA is used at doses >100 units/kg within a 24-hour period for ≥24 hours. Prescribing information for emicizumab carries a Boxed Warning for this risk [41]. If an aPCC is needed to treat breakthrough bleeding while receiving emicizumab (or within six months of discontinuation), the aPCC dose should be kept <100 units/kg in a 24-hour period; the patient should be monitored closely for thrombosis and TMA; and if one of these complications occurs, the aPCC should be discontinued.

- The recombinant activated factor VII (rFVIIa) product NovoSeven was not associated with these thrombotic events or TMA when used as the sole bypassing agent; similar data for the newer rFVIIa agent SevenFact are not available.

For those with low titer inhibitors (<5 BU), it may be possible to treat with high doses of factor VIII to overcome the inhibitor. (See 'Low titer inhibitor - High-dose factor infusion is an option' below.)

Inhibitors

Overview of patient with an inhibitor — Management of bleeding or surgery in a patient with an inhibitor (neutralizing alloantibody against infused factor) is especially challenging because inhibitors bind to the infused factor and render it ineffective. Inhibitors are much more likely to occur in individuals with hemophilia A and those with severe disease. Some patients may only become aware that they have an inhibitor in the midst of an acute bleeding episode or surgery, when factor infusions no longer raise factor activity levels to the expected range or if there is an allergic/anaphylactic reaction to the infusion, as seen in some patients with factor IX deficiency. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication".)

Any patient with an inhibitor is best treated in consultation with a comprehensive hemophilia treatment center, especially when a decision is being made to administer the factor in which they are deficient rather than to use bypassing therapy. This is particularly true for individuals receiving emicizumab. (See 'Patients with hemophilia A receiving emicizumab' above.)

Protocols for managing inhibitors should be available at each institution that cares for patients with hemophilia. The local hemophilia treatment center can assist in developing general protocols and protocols for specific patients. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Hemophilia treatment centers'.)

Management of bleeding or surgery in patients with inhibitors depends on the severity of bleeding and the type and titer of the inhibitor [7]. Inhibitors are diagnosed and classified by titer using the Bethesda assay, in which serial dilution of patient plasma is used to determine an

inhibitor titer in Bethesda units (BU). Inhibitors with a titer of <5 BU despite repeated factor infusions are referred to as low-responding inhibitors [42]. Any inhibitor ≥5 BU/mL at any time is considered high responding, even if the titer subsequently becomes undetectable due to lack of re-exposure. Classically, high-responding inhibitors rapidly increase upon re-exposure to infused factor in an anamnestic response that takes four to seven days. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication", section on 'Terminology and definitions'.)

Individuals with an inhibitor titer of ≥5 BU and those with an unknown titer but with a known high-responding inhibitor are less likely to be effectively treated with factor infusions in an emergency situation because the quantity of circulating antibody is likely too great to be overcome by factor infusion.

- For patients with a high-responding inhibitor whose current titer is <5 BU, it may be possible in some circumstances to treat them with factor coverage; this decision should only be made in consultation with a comprehensive hemophilia treatment center as anamnesis is expected.

- For a patient with a titer ≥5 BU with a high-responding inhibitor and serious bleeding with a need for major surgery, a bypassing product is used. (See 'High titer or high responding inhibitor - Use a bypassing product (rFVIIa or FEIBA)' below.)

- In an emergency setting when a patient is receiving factor infusions and factor activity level does not increase at one hour post-infusion (or bleeding does not respond to factor infusion and a factor activity level or inhibitor titer is not available), the patient should be treated as if they have a high titer/high-responding inhibitor until inhibitor testing with a Bethesda assay can be performed. The main caveats are that the original hemophilia A or B diagnosis is correct, the correct replacement factor was given, there is no heparin contamination in the sample, and the assay is performed correctly (including the use of a bovine substrate-based factor assay in individuals receiving emicizumab). (See 'High titer or high responding inhibitor - Use a bypassing product (rFVIIa or FEIBA)' below.)

- For patients with hemophilia A and an inhibitor who are receiving emicizumab, there is a risk of thrombotic microangiopathy when an aPCC is co-administered. (See 'Patients with hemophilia A receiving emicizumab' above and 'High titer or high responding inhibitor - Use a bypassing product (rFVIIa or FEIBA)' below.)

Other potential hemostatic therapies are under investigation but are not yet available for clinical use. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Prophylactic therapies under development'.)

Inhibitor eradication/immune tolerance induction should be addressed once the patient is stable and the bleeding episode has resolved or at the time of inhibitor development. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication", section on 'Immune tolerance induction'.)

High titer or high responding inhibitor - Use a bypassing product (rFVIIa or FEIBA) — A bypassing product is generally the first choice in a patient with hemophilia A or B who has a high titer inhibitor and requires treatment for bleeding or surgery. These clotting factor products contain an activated form of a clotting factor in the coagulation cascade. Activated factor VII (factor VIIa) can directly activate factor X, bypassing the need for factors VIII and IX. Available products include recombinant human factor VII (rFVIIa; including NovoSeven, NovoSeven RT, and SevenFact) and activated prothrombin complex concentrate (aPCC), such as FEIBA (factor eight inhibitor bypassing agent; the only aPCC available in most settings) (table 4). The rFVIIa products are also appropriate in individuals with hemophilia A who have critical bleeding while receiving emicizumab.

Both rFVIIa products and FEIBA contain activated clotting factors, and both are effective for hemostasis in hemophilia. For hemophilia B with an inhibitor, rFVIIa products are preferred because they do not contain factor IX; this is especially true in individuals with hemophilia B with an inhibitor who have experienced reactions or anaphylaxis upon exposure to factor IX. For hemophilia A, either product can be used, unless the patient is receiving emicizumab, in which case rFVIIa is used. If the patient has had a favorable response with one of these products, it is reasonable to use the same product again.

- **rFVIIa** – There are two rFVIIa products approved for individuals with hemophilia with inhibitors; they have different properties and different dosing (see "Recombinant factor VIIa: Administration and adverse effects", section on 'Available products and their properties'):
  - **NovoSeven** – Dosing of NovoSeven in individuals with hemophilia is typically 90 to 120 mcg/kg (rounded to the nearest vial size) every two to three hours until hemostasis is achieved and at three- to six-hour intervals after hemostasis has been restored [43].
  - **SevenFact** – SevenFact (a recombinant factor VIIa product licensed in 2020) in hemophilia can be dosed as follows for individuals ≥12 years of age; it is not licensed for younger children [44]:
    - **Severe bleeding** – 225 mcg/kg, followed if necessary six hours later with 75 mcg/kg every two hours.

- **Mild to moderate bleeding** – One dosing strategy is 75 mcg/kg repeated every three hours until hemostasis is achieved. An alternative dosing strategy is an initial dose of 225 mcg/kg, followed if necessary nine hours later with additional 75 mcg/kg doses every three hours as needed.

- **FEIBA** – Dosing of FEIBA is typically 50 to 100 units/kg every 6 to 12 hours, not to exceed 100 units/kg/dose or 200 units/kg/day [45]. Individuals receiving emicizumab are at risk for thrombotic microangiopathy (TMA) and thrombosis when treated with FEIBA; this is the reason for avoiding FEIBA at home in patients receiving emicizumab. Specific dosing guidelines should be followed, and patients should be monitored for signs and symptoms of thrombosis and thrombotic microangiopathy. (See 'Patients with hemophilia A receiving emicizumab' above.)

Dosing is adjusted based on clinical response (eg, cessation of bleeding) rather than laboratory testing [42]. Standard interval dosing is generally continued for at least 48 to 72 hours for severe bleeding or major surgery (generally 72 hours or longer for major surgery; shorter durations for minor surgery), followed by a taper in which the dosing interval is gradually increased. In cases of severe uncontrolled bleeding, it is important to remember that therapy with one bypassing product may be effective even if the other bypassing product has failed. Also, the patient may have a surgical, traumatic, or anatomic reason for continued bleeding that may need to be addressed surgically or endoscopically. In rare cases of ongoing joint bleeding, arterial embolization has been used [46].

Although FEIBA and/or rFVIIa may be lifesaving in individuals with severe hemophilic bleeding for whom factor replacement is ineffective, these products may be prothrombotic and thus attention to the occurrence of this potential complication should be maintained [47].

FEIBA is not the best choice for patients on emicizumab, due to the risk of thrombotic microangiopathy. If a patient with an inhibitor is receiving emicizumab and requires a bypassing agent, rFVIIa is used. (See 'Patients with hemophilia A receiving emicizumab' above and 'Inhibitors' above.)

In the FENOC (FEIBA NovoSeven Comparative) trial, 66 patients with hemophilia A (age range, 8 to 55 years; median inhibitor titer, 8.6 BU/mL) and a joint bleed were randomly assigned to receive one dose of FEIBA (85 units/kg) or two doses of rFVIIa (105 mcg/kg, twice); patients were then instructed to use the other product for their next joint bleed [48]. Participants were instructed to initiate the treatment within four hours of bleeding symptoms and to record the hemostatic efficacy at several time points. At six hours post-bleeding, the overall efficacy of FEIBA and rFVIIa were similar (81 and 79 percent, respectively); other time points and efficacy

measures did not show one product to be clearly superior. However, some individual patients derived greater efficacy from one product or the other, especially during the first 12 hours. Additional smaller randomized trials have also found comparable efficacy of FEIBA and rFVIIa in treating bleeding [49-51]. Perioperative use of bypassing agents has also been reported to show comparable efficacy of FEIBA and rFVIIa, although there is a greater body of experience with rFVIIa in surgical patients [7].

The rate of thrombosis with rFVIIa (NovoSeven RT) appears to be low when used for treatment of hemophilia with inhibitors. Trials and registries involving >12,000 patients used to support licensure found an overall thrombosis rate of 0.2 percent [52,53].

aPCCs may be associated with reactions due to activation of the complement and bradykinin systems when infused rapidly, as well as prothrombotic complications including venous thromboembolism, myocardial infarction, and disseminated intravascular coagulation [47]. These risks appear to be greater when an aPCC is used in trauma, surgery, serious bleeding, large, repeated doses, or prolonged administration. Individuals receiving emicizumab have additional risks including thrombotic microangiopathy (TMA) or thrombosis with aPCC doses >100 /kg in a 24-hour period. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Emicizumab efficacy and adverse events' and 'Patients with hemophilia A receiving emicizumab' above.)

Individuals with hemophilia B and an inhibitor can have anaphylactic reactions to factor IX, which is present in all PCCs and aPCCs. rFVIIa and aPCC have been used together in some patients, but this should only be done in the hospital by experienced clinicians at a hemophilia treatment center [54,55]. (See 'Inhibitors' above.)

Recombinant porcine factor VIII (hemophilia A) — Another option for a patient with hemophilia A and a high titer inhibitor is recombinant porcine factor VIII (susoctocog alfa; Obizur), which was initially developed for treating patients with autoantibodies to endogenous factor VIII (ie, acquired factor VIII deficiency [acquired hemophilia A]). (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)".)

This product has the theoretical advantage of achieving hemostasis with decreased cross reactivity to the neutralizing antibodies against human factor VIII and has been used effectively in individuals with hemophilia A and an inhibitor. However, cross-reacting antibodies to recombinant porcine factor VIII and porcine-specific sequence antibodies have been described.

- Use of recombinant porcine factor VIII in inherited hemophilia A is off-label in the United States.

- Recombinant porcine factor VIII has no role in hemophilia B.

We reserve recombinant porcine factor VIII for patients with hemophilia A and life-threatening or limb-threatening bleeding that cannot be controlled with a bypassing agent. When used, the product is dosed according to the weight of the patient and the standard dosing guidelines for acquired hemophilia A until a titer of anti-porcine factor VIII antibodies is available. Monitoring factor VIII levels is essential. Subsequent dosing is guided by standard factor VIII activity levels, with the exception of individuals receiving emicizumab, in whom a bovine substrate-based factor VIII activity assay must be used due to test interference with a standard factor VIII assay. (See 'Patients with hemophilia A receiving emicizumab' above.)

Plasmapheresis if a bypassing product is ineffective — Plasmapheresis may be useful in patients with a high titer inhibitor to acutely lower the inhibitor titer and allow transient use of replacement factor.

This approach is generally reserved for an individual with life-threatening or limb-threatening bleeding and an inhibitor titer >5 BU for whom bypassing therapy is not effective or recombinant porcine factor VIII is not available.

Details and complications are discussed separately. (See "Therapeutic apheresis (plasma exchange or cytapheresis): Indications and technology" and "Therapeutic apheresis (plasma exchange or cytapheresis): Complications".)

Low titer inhibitor - High-dose factor infusion is an option — An individual with bleeding and an inhibitor can be treated with high-dose factor infusion or a bypassing agent. The choice between these is individualized.

- **Bypassing agent** – A bypassing agent may be used if the inhibitor characteristics (whether it is high or low responding) are unknown, or in an emergency when it might be challenging to determine the amount of factor needed to bypass the inhibitor.

- **High dose factor infusion** – High dose factor infusion to overcome the inhibitor may be effective for patients with hemophilia A or B and a low titer (<5 BU) or low-responding inhibitor, as long as the patient does not have an infusion reaction to the replacement factor (reactions are most commonly seen with factor IX inhibitors).

  High-dose factor also may be useful for patients with high-responding inhibitors currently at a low titer or a titer lowered by plasmapheresis, with the understanding that this is only likely to be effective for a limited time period (four to seven days) and is likely to induce anamnesis [42].

Factor dosing to overcome an inhibitor has not been established from prospective trials. One approach is to administer the full replacement dose as described for a patient without an inhibitor above, plus an additional 50 percent correction for every BU of inhibitor. As an example, for a 60 kg patient with factor VIII deficiency treated with a standard half-life product such as Advate and an inhibitor of 2 BU who requires correction to 100 percent factor activity, the patient would be given the usual replacement dose (60 kg x 100 x 0.5 = 3000 international units of factor VIII) plus an additional dose (2 BU x 60 kg x 50 x 0.5 = 3000 international units of factor VIII) for a total dose of 6000 units of factor VIII.

This may be followed by bolus dosing, based on factor activity level measured 10 to 15 minutes after the infusion is completed, or by continuous infusion, at a starting rate adequate to compensate for altered pharmacokinetics based on the presence of an inhibitor, with dose adjustments based on factor activity levels.

Breakthrough bleeding during prophylaxis with a longer-lasting factor — Some patients use a longer-lasting factor for routine prophylaxis or acute bleeding and thus may have a longer-lasting product in their system or available for use. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Longer lasting recombinant factor VIII' and "Hemophilia A and B: Routine management including prophylaxis", section on 'Longer-lasting recombinant factor IX'.)

Management of bleeding is the same as for other patients, with factor infusion to maintain the factor level above the threshold determined necessary for the location and severity of bleeding. The calculations for dosing generally assume that the patient is at their baseline level (ie, calculations should be the same as for any other patients). (See 'Acute therapy for bleeding' above.)

For elective surgery, it is best to use the same longer-lasting factor that the patient uses at home, as this simplifies care and potentially simplifies issues of adverse events and the difficulty in determining how to ascribe these if changing products. Issues related to the use of longer-lasting products for surgical procedures are essentially the same as for standard half-life products and include use of appropriate monitoring assays for levels and assurance of adequate hemostatic levels. Use of longer-lasting products may reduce the number of infusions needed during and after procedures, depending on the product, the patient, and the individual half-life. It is important to use an assay for factor activity that is tailored to the specific factor being used [1].

Patient with mild hemophilia — Individuals with mild hemophilia (factor level between 5 and 49 percent) may require factor replacement therapy for acute bleeding, surgery, or invasive

procedures. It is important to remember that patients with mild hemophilia are also at risk of inhibitor development and should be followed closely during times of intensive replacement therapy. Knowledge of the specific genetic variant may help in predicting the risk of inhibitor development (see "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication", section on 'Patient characteristics'). These individuals should be managed by experts and a care team knowledgeable about hemophilia at a facility with access to factor should it be needed, similar to those with more severe deficiency.

- **Severe bleeding** – Patients with mild hemophilia A or B who have serious bleeding or require major surgery should be treated similarly to those with severe or moderate deficiency. (See 'Acute therapy for bleeding' above and 'Major surgery' above.)

- **Mild hemophilia A, minor bleeding** – Patients with mild hemophilia A may have a sufficient increase in factor VIII activity level upon administration of DDAVP (desmopressin; a synthetic analog of vasopressin/antidiuretic hormone that lacks pressor activity), which promotes release of endogenous factor VIII. A DDAVP test dose should be performed before use in an invasive procedure to assure an adequate hemostatic response, as discussed separately. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'DDAVP test dose for mild hemophilia A'.)

  DDAVP administration and adverse events are discussed below. (See 'DDAVP for mild hemophilia A' below.)

- **Mild hemophilia B, minor bleeding** – Mild hemophilia B cannot be treated with DDAVP because factor IX is not stored for release in platelets or endothelial cells. Patients with mild hemophilia B are treated with factor IX or other hemostatic therapies such as antifibrinolytic agents and/or topical therapies. (See 'Antifibrinolytic therapy for mucosal bleeding or surgery' below and 'Adjunctive local therapies' below.)

Resource-poor settings (no access to purified factor) — Purified factor products (virally inactivated plasma-derived concentrates or recombinant products) should be used whenever possible, to avoid potential transfusion-transmitted infection and transfusion reactions. However, individuals in resource-poor settings may not have access to these products. For such individuals, options include Fresh Frozen Plasma (FFP), or, for those with hemophilia A, Cryoprecipitate. Dosing is based on the factor concentration in the product, patient weight, and the desired factor level. One bag of Cryoprecipitate is made from approximately 250 mL of FFP and contains approximately 70 to 80 units of factor VIII in a volume of 30 to 40 mL (concentration of factor VIII in Cryoprecipitate, approximately 3 to 5 units/mL) [2]. One mL of FFP contains one unit of factor activity. A dose of 15 to 20 mL/kg will raise the factor VIII level by

approximately 30 to 40 percent and the factor IX level by approximately 15 to 20 percent (different increases are due to different volumes of distribution of factors VIII and IX). (See "Clinical use of plasma components", section on 'Plasma products' and "Cryoprecipitate and fibrinogen concentrate".)

ADJUVANT THERAPIES

Antifibrinolytic therapy for mucosal bleeding or surgery — Antifibrinolytic agents include tranexamic acid (TXA) and epsilon aminocaproic acid (EACA). These may be used in combination with factor replacement therapy for individuals with a mucosal source of bleeding, or as single agents in settings with mucosal bleeding that is less severe (eg, dental procedures). Topical administration to skin sites has also been reported [56].

These agents are most useful for stabilizing clots in areas of increased fibrinolysis such as the oral or nasal cavity (eg, dental bleeding, epistaxis) or for heavy menstrual bleeding in women with bleeding disorders [38,57]. Their mechanism of action is to inhibit fibrinolysis by inhibiting plasminogen activation in the fibrin clot, thereby enhancing clot stability. The decision between these agents is based on local preference; they have not been directly compared in patients with hemophilia and have appeared to have comparable efficacy in other settings.

- **TXA** – The usual oral dose is 25 mg/kg per dose every six to eight hours. Standard dosing for certain indications based on pill size may be useful, such as 1300 mg orally three times a day for heavy menstrual bleeding (use for up to five days, longer for some individuals) or 1000 to 1500 mg every 8 to 12 hours for epistaxis for up to 10 days (off-label dosing).

  The intravenous (IV) dose is 10 mg/kg, administered every six to eight hours.

- **EACA** – The usual dose is 75 to 100 mg/kg per dose every six hours (maximum single dose 3 to 4 g).

These drugs can be administered orally or intravenously. When given orally, they must be given three or four times over a 24-hour period because of their short half-lives. Dosing is often continued for several days, depending on the degree of injury and bleeding.

Antifibrinolytic agents should not be used for urinary tract bleeding due to the risk of obstruction by clots. Neither TXA nor EACA should be given simultaneously with an activated prothrombin complex concentrate (aPCC), as this will increase the risk of thromboembolism. If an antifibrinolytic agent and an aPCC are used, they should be separated by at least 12 hours [2]. There is some experience using TXA and recombinant factor VIIa (rFVIIa) together in the

surgical setting; consultation with a hemophilia treatment center is advised. (See 'High titer or high responding inhibitor - Use a bypassing product (rFVIIa or FEIBA)' above.)

Adjunctive local therapies — Other adjunctive hemostatic therapies include microfibrillar collagen, especially for bleeding in the oral cavity, and fibrin glue, which has been used following circumcision [58]. (See "Fibrin sealants".)

DDAVP for mild hemophilia A — DDAVP (desmopressin) is a synthetic analog of vasopressin (antidiuretic hormone]) that lacks pressor activity and may be effective for minor bleeding or certain elective procedures in patients with mild hemophilia A who have had a documented response to a test dose [19,58-62].

The test dose is generally performed as part of routine comprehensive care. If not done previously it should be performed at least one week prior to use for hemostasis, to allow review of the results, surgical planning, and communication among treating clinicians. Details of the test dose are described separately. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'DDAVP test dose for mild hemophilia A'.)

For those who have a response, a typical dose is 0.3 mcg/kg (maximum dose, 20 to 30 mcg), administered intravenously or subcutaneously; or as a nasal spray (Stimate), one puff (150 mcg) in one nostril in patients weighing <50 kg and two puffs (150 mcg in both nostrils) in patients weighing ≥50 kg.

For adults, a repeat dose may be given at 12 hours, and subsequent doses are often administered once daily, as long as the individual is under the supervision of a hemophilia expert. Administration of DDAVP is usually no longer than three days due to tachyphylaxis and hyponatremia risk. When using the nasal spray it is important to use the spray intended for hemostasis and not the spray for enuresis, which has a lower concentration.

DDAVP can increase the factor VIII level two- to fourfold. A patient with a baseline factor activity of 25 percent who has an increase to 50 percent may have adequate hemostasis with DDAVP in the setting of minor bleeding or procedures and thus avoid factor infusion. Tachyphylaxis may occur; the administration should be timed to provide the maximal response at the time of greatest bleeding risk, while limiting the number of doses.

The following caveats apply to DDAVP use:

- DDAVP is **not** effective for patients with severe hemophilia A (factor VIII activity <1 percent) because factor activity level cannot be increased sufficiently, and usually is not used in

individuals with moderate hemophilia A (factor VIII activity from 1 to 5 percent) for the same reason.

- DDAVP should **only** be used for mild bleeding for which a 30- to 60-minute delay is acceptable (90-minute delay for nasal spray) and a two- to fourfold factor VIII increase are likely to be sufficient for hemostasis. For more serious bleeding, factor VIII infusion should be used.

- DDAVP is **not** effective for patients with hemophilia B because factor IX is not stored in platelets or endothelial cells.

- DDAVP generally is not used in children under two years of age due to an increased risk of water retention that may result in a syndrome of inappropriate ADH (SIADH)-like picture and potentially cerebral edema and seizures [2]. If used in this age group, it should be done under hematologist supervision.

- DDAVP has antidiuretic activity and can cause hyponatremia, especially with prolonged use or excess free water intake. As a result, doses often are limited to once daily for three consecutive days, and **water intake is restricted**. The serum sodium concentration is monitored in hospitalized individuals, especially those receiving more than one or two doses of DDAVP.

- Additional adverse effects include facial flushing, headache, nausea, and tingling sensations. These can often be controlled by decreasing the rate of the infusion when administering the medication intravenously [63]. Cases of thrombosis have been reported, although a causal relationship is difficult to establish. Hypotension and hypertension have been reported but are not common and usually are mild. DDAVP is generally avoided in patients with a history of seizures, stroke, cardiovascular disease, and hypertension.

In rare patients with mild hemophilia A who have mild bleeding and wish to avoid factor infusion but have not been tested for DDAVP response, it may be reasonable to use DDAVP, especially if a post-dose factor VIII level is obtained; however, evidence to support this practice is lacking. Effective therapy should not be delayed in a bleeding patient, which may occur if the response to DDAVP is not documented.

COVID-19 OR OTHER CRITICAL ILLNESS

Individuals hospitalized with coronavirus disease 2019 (COVID-19) or other critical illness may require anticoagulation, either as prophylaxis against or treatment of acute thrombosis.

If a person with hemophilia is hospitalized with COVID-19, we favor treating with anticoagulation (prophylactic or therapeutic dose, depending on the clinical scenario). The following recommendations are based on a 2023 clinical practice expert guidance document by the EHA-ISTH-EAHAD-ESO (European Hematology Association, International Society on Thrombosis and Haemostasis, European Association for Hemophilia and Allied Disorders, and European Stroke Organization) [64]. We previously used the interim guidance from the World Federation of Hemophilia and that of other experts for treatment of individuals with hemophilia and COVID-19 [1,65-68].

Prophylaxis with factor infusions or other therapy (such as emicizumab in hemophilia A) should be continued. For those receiving emicizumab, factor VIII can be added; for those receiving factor VIII, the dose can be intensified. Individuals receiving emicizumab at a stable dose do not require infusions of factor VIII if not hospitalized and stable at home.

Other considerations include [66]:

- Target factor levels in persons with hemophilia hospitalized with COVID-19 are individualized; for those receiving prophylactic-dose anticoagulation, we generally include a trough level of at least 20 percent and avoidance of peak levels above 100 percent [64].
- If full (therapeutic-dose) anticoagulation is required for treatment of thrombosis, the trough factor level can be maintained between 20 and 100 percent for hemophilia A and between 20 and 80 percent for hemophilia B.
- Monitoring of anticoagulation is important, with the assay(s) appropriate to the anticoagulant.
- Factor VIII levels in individuals with hemophilia B or mild hemophilia A may be increased due to acute inflammation. Monitoring of factor levels before and during therapy is essential in all individuals with hemophilia.
- Hemophilia by itself does not affect D-dimer levels; D-dimer, fibrinogen, and platelet count can be used for the assessment of disease severity similar to individuals without hemophilia.

Details of anticoagulation in COVID-19 are presented separately. (See "COVID-19: Hypercoagulability", section on 'Management'.)

Although experience is more limited with other acute or critical illnesses, we would use a similar approach in which the appropriate clotting factor is administered or other therapy such as emicizumab is continued to allow anticoagulation if needed.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hemophilia A and B".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hemophilia (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Serious bleeding** – Serious or life-threatening bleeding (intracranial, ocular, serious trauma) requires urgent treatment with factor concentrate, targeting a factor activity of 80 to 100 percent (table 1). If available, give the patient's own factor product; recombinant factor is a reasonable alternative. (See 'Serious, life-threatening bleeding and head trauma' above.)

  Hemophilia treatment center (HTC) involvement or equivalent expertise is essential. However, life-saving treatments should not be delayed while contacting the HTC or awaiting their response.

  - **Hemophilia A (including individuals on emicizumab) without an inhibitor** – Give 50 units/kg of factor VIII (half-life is at least 8 to 12 hours) (table 2).

- **Hemophilia B without an inhibitor** – Give 100 to 140 units/kg of factor IX (half-life is at least 18 to 24 hours) (table 3). If there is time for calculation, dosing can be based on the product's volume of distribution (Vd): Dose (units) = % correction x Vd x weight (kg), using the Vd for the specific product.

- **Inhibitors** – Inhibitors (neutralizing antibodies) will inactivate infused factor. (See 'Overview of patient with an inhibitor' above.)

  - For a high titer and high-responding inhibitor (≥5 Bethesda units) and serious bleeding or major surgery, we recommend a bypassing product (FEIBA or recombinant factor VIIa) rather than factor concentrate (**Grade 1C**). Porcine factor VIII is another option for hemophilia A not treated with a bypassing agent. Plasmapheresis may be used to lower the inhibitor titer in life-threatening bleeding if a bypassing agent is ineffective. (See 'High titer or high responding inhibitor - Use a bypassing product (rFVIIa or FEIBA)' above and 'Recombinant porcine factor VIII (hemophilia A)' above and 'Plasmapheresis if a bypassing product is ineffective' above.)

  - For a low-responding inhibitor, treatment decisions are individualized. Options include a bypassing agent, porcine factor VIII (for hemophilia A), or high dose factor concentrate. (See 'Low titer inhibitor - High-dose factor infusion is an option' above.)

  - Individuals with hemophilia A with an inhibitor who are receiving emicizumab can be treated with rFVIIa. FEIBA is not combined with emicizumab due to risk of thrombosis.

  Subsequent dosing depends on peak and trough factor activity and bleeding site and severity. (See 'Monitoring and dose calculation for subsequent doses' above.)

- **Joint bleeding** – Infuse factor within two hours of bleed identification; target factor activity at approximately 50 percent (trauma may require higher targets). Repeated factor infusions assure adequate resolution. (See 'Hemarthroses' above.)

- **Surgery** – Managed in consultation with the HTC, including (see 'Elective surgery' above):

  - Coordination among patient/family/caregivers and relevant clinicians.
  - Preoperative inhibitor screening.
  - Determining desired factor activity.

- Planning for monitoring and factor administration (special considerations for individuals receiving emicizumab).

Certain sites may be especially serious due to their location and possibility of causing airway compromise (retropharyngeal bleeding from tonsillectomy or impacted mandibular wisdom tooth extraction).

- **Adjuvant therapies**

  - **Antifibrinolytic therapy** – For bleeding or surgery in areas of increased fibrinolysis (oral, nasal, gastrointestinal, gynecologic), we suggest an antifibrinolytic agent (**Grade 2C**). Tranexamic acid (TXA) or epsilon aminocaproic acid (EACA) can be used. Duration of therapy is individualized. This may be the sole therapy required (eg, mild hemophilia, dental procedure). Some individuals may reasonably omit antifibrinolytic therapy if they are receiving factor infusions. (See 'Antifibrinolytic therapy for mucosal bleeding or surgery' above.)

  - **DDAVP** – DDAVP (desmopressin) may be effective for elective procedures in mild hemophilia A (factor VIII activity 5 to 40 percent), provided there was a previous documented response to a test dose. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'DDAVP test dose for mild hemophilia A' and 'DDAVP for mild hemophilia A' above.)

- **Hospitalization (COVID-19 or other acute illness)** – Individuals hospitalized with a critical illness such as COVID-19 may require anticoagulation as prophylaxis or treatment of acute thrombosis. If a person with hemophilia requires anticoagulation, factor infusions or other therapy (such as emicizumab in hemophilia A) should be continued or started if needed. (See 'COVID-19 or other critical illness' above.)

- **WFH Guidelines** – Our approach is consistent with 2020 World Federation of Hemophilia Guidelines (https://www1.wfh.org/publications/files/pdf-1863.pdf).

- **Other aspects of care** – (See "Clinical manifestations and diagnosis of hemophilia" and "Hemophilia A and B: Routine management including prophylaxis" and "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication" and "Genetics of hemophilia A and B".)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges extensive contributions of Donald H Mahoney, Jr, MD, and Lawrence LK Leung, MD, to earlier versions of this topic review.

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Topic 1314 Version 74.0

GRAPHICS

Treatment of bleeding in hemophilia

	Hemophilia A	Hemophilia B
Major/severe bleeding* Raise factor level to 80 to 100%	Factor VIII dose of approximately 50 units/kg	Factor IX dose of approximately 100 to 120 units/kg
Hemarthrosis Raise factor level to 40 to 50%	Factor VIII dose of approximately 25 units/kg	Factor IX dose of approximately 50 to 60 units/kg

This table is a general guide and does not replace clinical judgment in determining the severity of bleeding, risk of morbidity, factor dosing, and need for other treatments. Mucosal bleeding can be treated with antifibrinolytics or local hemostatic therapies concomitantly with factor infusion. Patients with mild hemophilia A and minor bleeding may be treated with DDAVP if they have previously demonstrated a response. Patients with inhibitors may require a bypassing agent such as recombinant activated factor VII (rFVIIa) or FEIBA. Do not use antifibrinolytics with FEIBA concomitantly. Refer to UpToDate for additional information about management of bleeding in patients with hemophilia.

FEIBA: Factor eight inhibitor bypassing agent.

* Examples of major bleeding include bleeding affecting the central nervous system, airway, hip, deep muscle with neurovascular injury, or abdomen; bleeding that cannot be controlled with local therapies, or bleeding necessitating transfusion.

Graphic 110820 Version 1.0

Selected available factor VIII products for patients with hemophilia A

Product name	Half-life (hours)*	Characteristics
Standard half-life products[¶]		
Advate	9 to 12	Recombinant
Hemofil M	15	Plasma-derived; mAb-purified
Kogenate FS	11 to 15	Recombinant
Koate (previously called Koate DVI)	16	Plasma-derived; chromatography-purified
Kovaltry	12 to 14	Recombinant
Novoeight	8 to 12	Recombinant
Nuwiq	12 to 17	Recombinant
Recombinate	15[Δ]	Recombinant
Xyntha	8 to 11	Recombinant
Longer-lasting products		
Adynovate	13 to 16	Recombinant; PEGylated
Afstyla	10 to 14	Recombinant; single chain
Altuviiio	40 to 48	Recombinant; Fc-VWF-XTEN fusion
Eloctate	13 to 20	Recombinant; Fc fusion
Esperoct	17 to 22	Recombinant, glycoPEGylated
Jivi	17 to 21	Recombinant; PEGylated

This table is intended as a guide for rapid identification of the product the patient is using and its characteristics and should not be used to select a product or calculate dosing. Refer to prescribing information in the product insert and to UpToDate for the use of factor replacement in patients with hemophilia. The plasma-derived products listed here are ultra-high purity (mAb-purified) or high purity (chromatography-purified).

FS: formulated with sucrose; mAb: monoclonal antibody; Fc: fragment crystallizable; VWF: von Willebrand factor; XTEN: half-life extension polypeptides; PEG: polyethylene glycol.

* Half-lives are approximate. Half-lives are generally shorter for children than adults when assessed in pharmacokinetic studies. The half-life of factor VIII products without modifications to extend half-life is considered to be approximately 12 hours. The half-life should be determined for the individual patient. Refer to product information and institutional guidelines for additional dosing and monitoring information.

¶ Monoclate-P was discontinued in early 2018. Helixate FS manufacturing was discontinued in 2018, with supply available through early 2019.

Δ Adults only.

Graphic 109838 Version 10.0

Selected available factor IX products for patients with hemophilia B

Product name	Half-life (hours)*	Characteristics
Standard half-life products		
AlphaNine SD	18¶	Plasma-derived; solvent/detergent treated
BeneFIX	16 to 19	Recombinant
Ixinity	24Δ	Recombinant
Mononine	23¶	Plasma-derived; mAb purified
Rixubis	23 to 26	Recombinant
Longer-lasting products		
Alprolix	54 to 90	Recombinant; Fc fusion
Idelvion	104¶	Recombinant; albumin fusion
Rebinyn	103 to 115	Recombinant; glycoPEGylated

This table is intended as a guide for rapid identification of the product the patient is using and its characteristics. Refer to the product information and to UpToDate for the use of factor replacement in patients with hemophilia.

SD: solvent/detergent treated; mAb: monoclonal antibody.

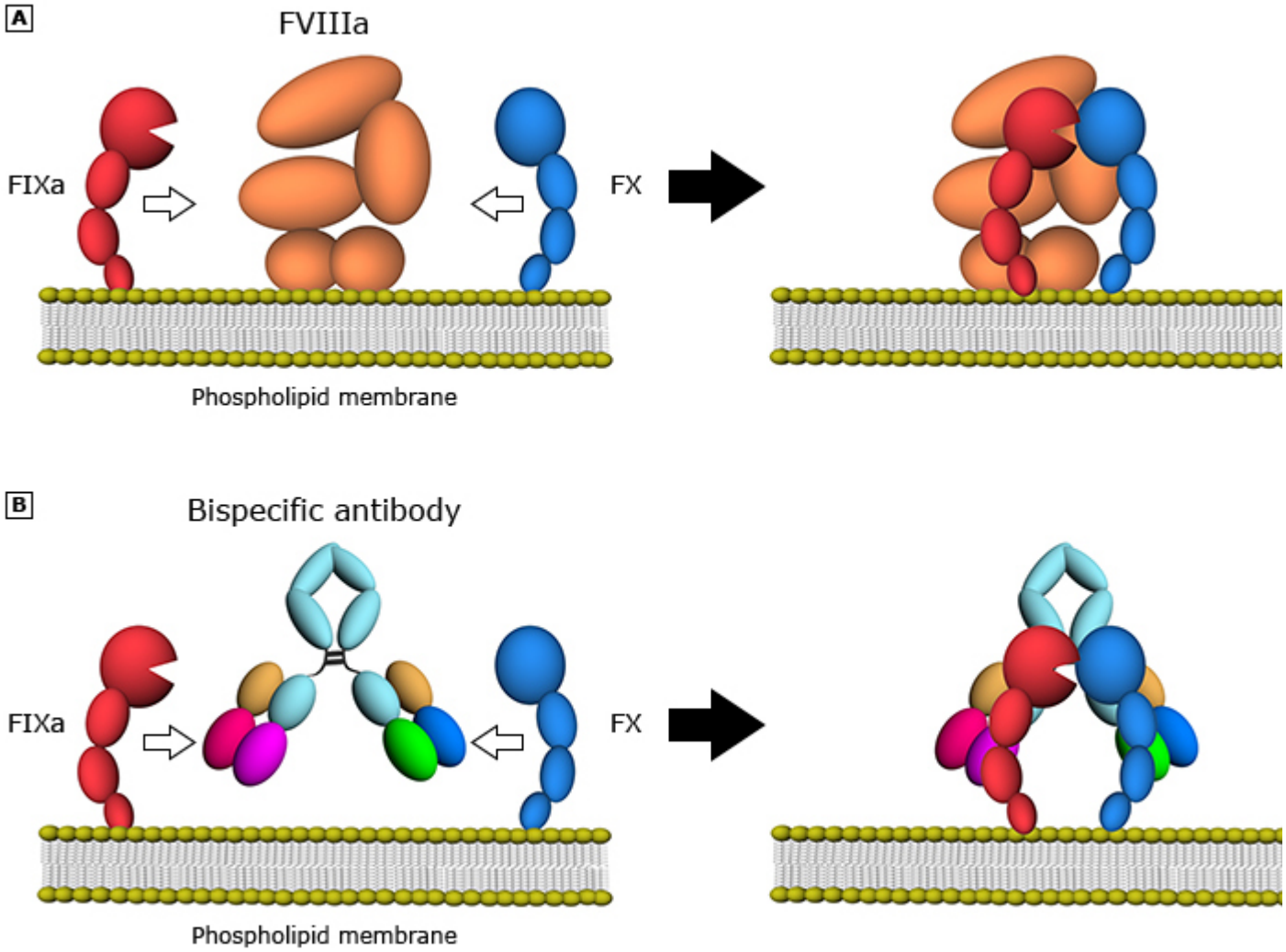
* Half-lives are **approximate**. Half-lives are generally shorter for children than adults when assessed in pharmacokinetic studies. The half-life of factor IX products without modifications to extend half-life is considered to be approximately 24 hours. The half-life should be determined for the individual patient. Refer to product information and institutional guidelines for additional dosing and monitoring information.

¶ Adults only.

Δ 12 years and older.

Graphic 109839 Version 4.0

Bispecific antibody that could be used to replace the function of FVIIIa



Refer to UpToDate content on treatment of hemophilia for further details.

(A) In normal hemostasis, FVIIIa (orange) forms a complex with FIXa (red) and promotes interaction between FIXa and FX (blue) by binding to both factors on the phospholipid membrane.

(B) A bispecific antibody that can simultaneously bind to FIXa (red) and FX (blue) could mimic the activity of FVIIIa and promote interaction between FIXa and FX on the phospholipid membrane.

FVIIIa: activated coagulation factor VIII (eight); FIXa: activated coagulation factor IX (nine); FX: coagulation factor X (ten).

From: Sampei Z, Igawa T, Soeda et al. Identification and Multidimensional Optimization of an Asymmetric Bispecific IgG Antibody Mimicking the Function of Factor VIII Cofactor Activity. PLoS One 2013; 8:e57479. Available at: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0057479 (Accessed on May 10, 2016). Copyright © 2013 Sampei et al. Reproduced under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Graphic 107801 Version 2.0

PCC products available in the United States*

Unactivated prothrombin complex concentrates (PCCs)	
4 factor: ▪ Kcentra	Contains inactive forms of 4 factors: Factors II, VII, IX, and X Also contains heparin
3 factor: ▪ Profilnine	Contains inactive forms of 3 factors: Factors II, IX, and X Contains little or no factor VII Does not contain heparin
Activated prothrombin complex concentrate (aPCC)	
4 factor: ▪ FEIBA	Contains 4 factors: Factors II, VII, IX, and X. Of these, only factor VII is mostly the activated form¶ Does not contain heparin

The table lists 4-factor and 3-factor PCC products available in the United States. Kcentra is available as Beriplex in Canada. Bebulin (a 3-factor PCC) was discontinued in 2018 due to decreased demand for the product. Potency is determined differently for different products; refer to product information. All PCCs are plasma derived and contain other proteins, including anticoagulant proteins (proteins C and S). Unactivated factors are proenzymes (inactive precursor proteins). Activated factors have higher enzymatic activity. Refer to UpToDate topics for use of these products.

US: United States; PCC: prothrombin complex concentrate; FEIBA: factor eight inhibitor bypassing activity.

* Other 4-factor PCCs available outside the US include Octaplex and Cofact Proplex.

¶ Single-factor recombinant activated factor VII (rFVIIa) products are also available.

Graphic 94210 Version 8.0