Hemophilia A and B: Routine management including prophylaxis

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INTRODUCTION

Hemophilia A (factor VIII [factor 8] deficiency) and hemophilia B (factor IX [factor 9] deficiency) are X-linked inherited coagulation factor deficiencies that result in lifelong bleeding disorders. The availability of factor replacement products has dramatically improved care for individuals with these conditions. However, the severity and frequency of bleeding is variable, the optimal management is complex, new therapies are being introduced rapidly, and many challenging management decisions continue to arise.

This topic review discusses routine management of individuals with hemophilia A and B, including preventive and comprehensive care at various ages, and decisions regarding prophylactic factor infusion.

Separate topic reviews discuss diagnosis, treatment of bleeding, surgery, inhibitor eradication, age-related comorbidities and complications, and genetics of hemophilia.

- **Surgery and treatment of bleeding** – (See "Acute treatment of bleeding and surgery in hemophilia A and B".)
- **Inhibitor eradication** – (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication".)

- **Investigational approaches** – (See "Gene therapy and other investigational approaches for hemophilia".)
- **Diagnosis** – (See "Clinical manifestations and diagnosis of hemophilia".)
- **Complications and comorbidities** – (See "Chronic complications and age-related comorbidities in people with hemophilia".)
- **Genetics** – (See "Genetics of hemophilia A and B".)

The evaluation and management of individuals with other inherited coagulation disorders and acquired factor deficiencies are also presented in detail separately. (See "Rare inherited coagulation disorders" and "Factor XI (eleven) deficiency" and "Disorders of fibrinogen" and "Clinical presentation and diagnosis of von Willebrand disease" and "Acquired hemophilia A (and other acquired coagulation factor inhibitors)".)

ROUTINE/COMPREHENSIVE CARE

The optimal management of people with hemophilia is complex. Interventions directed at reducing complications of hemophilia and its treatment are paramount. At the same time, routine health maintenance and comprehensive care is critical to decrease other health risks that have the potential to become more complicated due to the underlying bleeding disorder.

Integrated care should be instituted as soon as the diagnosis of hemophilia is made [1]. This includes decisions about prophylaxis with factor concentrates or other therapeutics, methods to minimize bleeding risk, and counseling regarding psychosocial issues and disease inheritance. Education about the disease is important for families and caregivers, especially those with newborns with a new hemophilia diagnosis, since the newborn will be the first person with hemophilia in approximately one-third of kindreds. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Epidemiology' and "Clinical manifestations and diagnosis of hemophilia", section on 'Initial presentation'.)

Hemophilia treatment centers — Designated hemophilia treatment centers (HTCs) have been established in many parts of the world to provide multidisciplinary care for individuals with hemophilia and other bleeding disorders. HTCs were established in the United States in the mid-1970s; there are approximately 140 active HTCs in the United States. HTCs are also present in most countries in the developed world [2].

Listings of HTCs are available online:

- **United States** – The Centers for Disease Control and Prevention (CDC) lists United States HTCs on their website: https://dbdgateway.cdc.gov/HTCDirSearch.aspx.

- **International** – The World Federation of Hemophilia has a searchable directory of HTCs: https://wfh.org/find-local-support/#HTCs.

The United States National Hemophilia Foundation (www.hemophilia.org) and American Thrombosis and Hemostasis Network (athn.org) provide additional resources.

Comprehensive HTCs provide a wide range of services, which include testing for bloodborne viral infections and access to appropriate care and therapy. The multidisciplinary team provides coordinated chronic disease management and expert hemophilia care, risk reduction counseling, and ongoing education of patients and families. HTCs also manage physical therapy, social work, genetic counseling, home therapy and preventive services, and more, and they work closely with hemophilia consumer organizations.

The benefit of HTCs was demonstrated in a 2000 study that compared mortality in 2950 individuals with hemophilia (7575 person-years of observation) according to the site of care (HTC or non-HTC) [3]. This study documented a significant improvement in life expectancy associated with HTC-based care (relative risk [RR] of death 0.6, 95% CI 0.5-0.8) despite HTCs caring for a population with more severe disease and associated co-morbidities.

Newborn care — The majority of infants with hemophilia present with a known family history; advance noninvasive fetal sex determination is used to guide labor and delivery. However, a sizable minority of affected individuals have an unexpected diagnosis, either due to a de novo mutation in the mother, or lack of transmission of knowledge of risk or genetic analysis of at-risk individuals within a family. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Initial presentation'.)

- For a male child born to a known female carrier, multidisciplinary planning is required to address maternal and fetal bleeding risks, method of delivery, and avoidance of interventions such as fetal scalp electrodes, fetal venous sampling, and operative vaginal delivery (eg, use of forceps, vacuum extraction). Intramuscular vitamin K and heel stick for standard neonatal screening tests should be performed by experienced staff with additional pressure held at the site. These issues are discussed in detail separately. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Method of delivery and anesthesia'.)

- Recommended neonatal immunizations (eg, hepatitis B vaccine) should be administered; the smallest gauge needle should be used, and pressure and ice applied to the site for three to five minutes post injection. (See 'Immunizations' below.)

- Invasive procedures such as circumcision should be deferred for any male child born to a hemophilia carrier or any newborn with unexplained bleeding until a diagnosis such as hemophilia is confirmed or excluded. Circumcision is a controversial and an individual or important decision for some families and is a religious ritual for certain groups such as Muslims and Jews [4,5]. An approach to this and other invasive procedures if the patient is diagnosed with hemophilia is presented separately. (See "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'Circumcision'.)

- Diagnostic testing for the relevant factor level (factor VIII [8] for hemophilia A or factor IX [9] for hemophilia B) is performed using cord blood (preferred) or a venous sample, with comparison to age-appropriate normal controls. In cases without a family history, von Willebrand factor antigen is also required in addition to the factor VIII level since von Willebrand disease (VWD) is also in the differential diagnosis. Some individuals with mild factor VIII deficiency may require repeat testing, since factor VIII is increased at birth and a mild deficiency may be missed. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Diagnostic evaluation'.)

Immunizations — Recommended immunizations should be given at age-appropriate intervals to individuals with hemophilia.

Modifications to reduce the risk of bleeding include:

- For individuals receiving factor prophylaxis, timing the vaccine to occur when factor levels are high (soon after factor administration) [6]. This does not apply to emicizumab, since the steady state level is more consistent.
- Limiting the number of injections per limb.
- Use of the smallest gauge needle.
- Application of pressure and/or ice to the site for three to five minutes post injection. We use direct pressure for five minutes followed by ice for five minutes.

These risk reduction measures are especially relevant for intramuscular vaccines. In a series of 29 children who received 64 doses of an intramuscular vaccine without factor or emicizumab prophylaxis, there were no bleeding episodes [7]. An associated literature review of 702 intramuscular vaccines, there were 17 instances of bleeding after vaccination, one of which required factor treatment. Bleeding was most likely in adults >50 years. Based on their findings, the authors concluded that infants could receive intramuscular vaccines without prophylaxis.

Standard vaccination schedules and other issues such as avoidance of live vaccines when there is an immunocompromised member of the household, are presented separately. (See

"Poliovirus vaccination" and "Standard immunizations for children and adolescents: Overview", section on 'Routine schedule'.)

Dental care — Appropriate oral hygiene and regular dental care is essential for individuals with hemophilia to prevent gingival and dental disease, which increase the risk of bleeding. Early infant dental intervention is recommended to teach proper brushing and ensure adequate household water fluoridation. The teeth should be cleaned routinely, and anticipated problem areas that may cause bleeding should be discussed. An example is frenulum injury as a cause of bleeding in young children. Management of dental procedures is discussed separately. (See "Acute treatment of bleeding and surgery in hemophilia A and B".)

Exercise and athletic participation — An appropriate exercise regimen should be encouraged as a daily routine. Benefits include maintenance of a healthy weight, cardiovascular risk reduction, and positive effects on strength, flexibility, balance, and bone density, all of which contribute to decreased stress on joints. Exercise is also valuable for socialization and psychological health, which may be affected by a chronic condition such as hemophilia [8]. Children with hemophilia are vulnerable to loss of physical conditioning, reduced bone density, and excessive weight gain/obesity due to activity restrictions [9,10]. The role of an exercise program is best discussed early to support positive lifelong habits and health.

The World Federation of Haemophilia Working Group on Physical Therapy and the National Hemophilia Foundation Physical Therapy Committee have developed patient educational materials that quantify some of the musculoskeletal benefits and risks of organized and individual physical exercise [11,12]. The best approach to defining individual athletic regimens involves consultation between the staff at a local HTC; the patient; and for minor children, the parents and caregivers.

Ideal activities are those that reflect the individual's preferences, abilities, and local resources, and include non-contact sports such as swimming, walking, golf, tennis, bicycling, archery, and table tennis, and supervised group activities [13]. In one series of 37 children with severe hemophilia A or B who were receiving prophylactic factor infusions, the frequency of joint bleeding was low (<1 bleed or injury per season) and did not differ between high impact activities (eg, basketball, karate, skateboarding) and low impact activities (eg, cycling, swimming, hiking) [9]. Examples of high and low impact sports are listed in the table (table 1).

Consultation with a specialist regarding protective gear, splints, and prophylactic factor infusions timed around the activities should be initiated early and as needed. Additional

information about specific activities is provided in a publication from the National Hemophilia Foundation [12].

Medicines to avoid — Medicines that increase the risk of bleeding, including anticoagulants, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDs) should generally be avoided in patients with hemophilia. Pain can be treated with local measures (eg, cold packs, immobilization, splinting), acetaminophen, or codeine. Cardiovascular disease prevention should focus on diet, exercise, smoking avoidance, and control of hypertension and hypercholesterolemia.

Use of antithrombotic drugs may be associated with an increased risk of bleeding in patients with hemophilia. Therefore, their use should only be instituted in consultation with a comprehensive hemophilia treatment center. Selected examples include the following, but this is not an exhaustive list.

- Individuals with cardiovascular disease may be treated with aspirin or an anticoagulant if the benefits are thought to outweigh the risks, with consideration given to institution of a factor replacement regimen that provides protection. (See "Chronic complications and age-related comorbidities in people with hemophilia", section on 'Cardiovascular disease'.)

- Some patients with arthropathy can use cyclooxygenase (COX)-2 inhibitors. (See "Overview of COX-2 selective NSAIDs".)

It is also important to discuss herbal remedies and over-the-counter supplements such as fish oil, which may increase bleeding risk and are not always volunteered by the patient [14]. These may not need to be strictly avoided, but the physician should be aware of their use and have a discussion about the possible impact on bleeding risk.

Planning for invasive procedures — For individuals with hemophilia who are undergoing elective surgery, collaboration between the surgeon, anesthesiologist, hematologist, and laboratory and transfusion medicine services should occur, with sufficient time to allow a smooth surgical course in which factor levels can be monitored and replacement therapy administered on time. The specific factor dosing schedule, appropriate target factor levels, and duration of therapy depend on the individual patient and procedure being performed; some individuals may be able to use products other than clotting factor (eg, DDAVP for mild hemophilia A). These issues are discussed in detail separately. (See "Acute treatment of bleeding and surgery in hemophilia A and B".)

DDAVP test dose for mild hemophilia A — DDAVP (desmopressin) is a synthetic analog of vasopressin (antidiuretic hormone) that promotes release of factor VIII and its carrier protein

von Willebrand factor (VWF) from storage pools in platelet granules and endothelial cells. For individuals with mild hemophilia A (factor VIII activity level between 5 and 40 percent), a DDAVP test dose can be given to determine whether DDAVP is effective in that individual, and if so, whether it can be used to raise the factor VIII level in the setting of mild bleeding or invasive procedures. This should be done at least one week before a planned procedure, since tachyphylaxis occurs. Usually it is done as part of routine comprehensive care so that DDAVP can be used for a variety of mild bleeding scenarios, including surgical, traumatic, or spontaneous. (See "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'Patient with mild hemophilia'.)

The DDAVP test dose should be performed when the individual is well. It involves a baseline measurement of factor VIII activity level, followed by administration of DDAVP, followed by measurement of a post-DDAVP factor VIII activity level. DDAVP can be administered intravenously, subcutaneously, or intranasally (with a nasal spray).

Dosing and post-DDAVP factor VIII level measurement is as follows:

- **Intravenous DDAVP** – Give 0.3 mcg/kg (maximum dose, 20 to 30 mcg). The intravenous form is diluted in 50 mL of normal saline and infused over 20 to 30 minutes. Obtain the post-DDAVP factor VIII level approximately 60 minutes after DDAVP administration. The dose maximum of 20 to 30 mcg is commonly used in the United States due to concerns about increasing toxicity and diminishing efficacy at higher doses, although there are no data directly comparing different dose caps in a large sample of patients.

- **Subcutaneous DDAVP** – Give 0.3 mcg/kg (maximum dose, 20 to 30 mcg), divided so that no injection is >2 mL. The injections are given in the subcutaneous tissue of the lower abdomen, anterior thigh, or deltoid, using a 30-gauge needle(s). Pressure should be applied to each injection site for 2 to 5 minutes.

- **Intranasal DDAVP** – When using the nasal spray, it is important to use the product intended for hemostatic therapy (Stimate) rather than the product for enuresis, since the dose is higher for bleeding disorders (1.5 mg/mL rather than 0.01 percent). Give 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. Obtain the post-DDAVP factor VIII level approximately 90 minutes after DDAVP administration.

Factor VIII activity levels are checked 90 minutes after the start of intravenous administration (60 minutes after completion of the infusion) or 90 minutes after subcutaneous injection.

In individuals for whom this is effective, an approximately two- to fourfold increase in factor VIII activity level is expected at approximately 60 minutes after an infusion or 90 minutes after an intranasal dose, with the response persisting for 6 to 12 hours [15]. Some individuals have a lower or greater increase.

Additional doses may be given; however, tachyphylaxis (waning efficacy with multiple infusions) may occur with repeated dosing, and dosing at intervals shorter than 24 hours may be associated with increased risk of water retention. One study of serial DDAVP doses (one dose per day) found a 30 percent lower peak level in factor VIII increase between the first and second doses of DDAVP [16].

The likelihood of response to DDAVP has been assessed in several case series. As examples:

- In a review of intravenous DDAVP test doses given to 62 boys with mild hemophilia A at one institution, 29 (47 percent) had at least a twofold increase in factor VIII level one hour after administration of DDAVP [17]. The likelihood of response was greatest in those with higher baseline factor levels and with increasing age; an additional seven boys who did not have an initial response and were retested approximately five years later did have a response upon retesting. Another report that included 20 patients with mild hemophilia A documented DDAVP responses in 75 percent [18].

- In a study of 22 individuals (11 with hemophilia A and 11 with von Willebrand disease [VWD]) who had a documented response to intravenous DDAVP at 60 minutes and were subsequently tested for the response to intranasal DDAVP (Stimate) at 90 minutes, all of the patients with hemophilia A had increases in factor VIII levels (median increment of 30 percent [from 17±11 percent to 50±25 percent]) [19]. This was less than the median increment with intravenous DDAVP of 62 percent, but 9 of 11 had a final factor VIII level above 20 percent, which is minimally hemostatic in specific instances. A study in 10 volunteers without hemophilia documented that intravenous and intranasal DDAVP produced similar responses, supporting the usefulness of the intranasal route [20].

DDAVP is generally reserved for minor bleeding or minor invasive procedures in individuals with mild hemophilia A. Severe, life-threatening bleeding should be treated with factor infusion because the response to DDAVP is not immediate and may not raise the factor VIII level for optimal hemostasis. Individuals with moderate to severe hemophilia A (factor VIII level <5 percent) are unlikely to derive benefit from DDAVP because the incremental increase in factor VIII level would be insufficient for hemostasis. Rarely, an individual with a factor VIII level in the moderately deficient range (ie, levels near 5 percent) might be able to use DDAVP if they prefer, as long as testing demonstrates an adequate DDAVP response. Details of DDAVP administration

to treat bleeding, including the importance of limiting free water to prevent hyponatremia, are presented separately. (See "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'DDAVP for mild hemophilia A'.)

DDAVP is **not** used in hemophilia B because factor IX is not present in storage pools.

Obstetric care and preconception counseling — Obstetric care, including preconception counseling, prenatal evaluation, delivery, and neonatal diagnosis, are discussed in detail separately. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Obstetric considerations'.)

Travel — Appropriate planning for travel should occur in individuals with hemophilia regardless of level of severity. At a minimum, an emergency supply of hemostatic replacement therapy should be kept with the patient during travel. In addition, knowledge of the available HTC either along the route or at the final destination is needed. A letter from the primary HTC detailing the patient's diagnosis and treatment along with contact information for the treating hematologist is very useful. The use of a medic alert bracelet can be lifesaving in emergency situations. For air travel, a prescription listing medications can facilitate passage through airport security, especially if syringes and needles are carried.

PROPHYLAXIS TO REDUCE BLEEDING EPISODES

Overview of decision-making — A number of decisions need to be made regarding routine factor replacement therapy [21-23]:

- Should the individual receive prophylactic or on-demand therapy?
- Should prophylaxis be instituted at a very young age (before bleeding episodes occur) or deferred until a specific time?
- Should prophylaxis be continuous or intermittent?
- What is the best prophylactic therapy for the patient (factor replacement product [plasma-derived, recombinant, or long acting] or newer agents with different mechanisms of action, such as emicizumab)?
- Does the individual require a central venous catheter?
- Can prophylaxis ever be discontinued?

Prophylaxis versus on-demand therapy — Prophylactic therapy (factor administration in the absence of bleeding) (table 2) is highly effective in reducing bleeding and long-term complications of bleeding such as chronic arthropathy in people with hemophilia, especially those with severe factor deficiency or phenotype [24]. Prophylactic therapy also reduces the

incidence of intracerebral hemorrhage (ICH) which is less common than joint bleeding but potentially very devastating [25]. Additional advantages include reduced hospitalizations, increased ability to participate in activities, and reduced absenteeism from school or work [26].

However, the costs and burdens of using clotting factor replacement for prophylaxis are high, including the need for recurrent venous access that may require placement of a central venous catheter (which can result in an increased risk for infection and thrombosis), the need to adhere to recurrent intravenous factor infusions, the overall cost of care, and interference with family life and normal activities [27,28]. Emicizumab is increasingly used for prophylaxis in individuals with hemophilia A, with and without inhibitors. (See 'Emicizumab for hemophilia A' below.)

These benefits and risks, along with patient values and preferences, inform decisions regarding whether and when to start prophylaxis. Mild or moderate factor deficiency with a decreased clinical bleeding phenotype may be important decision-making points favoring on-demand therapy (factor given only in the setting of acute bleeding or surgery, also called episodic therapy). Individuals may decide to change from on-demand to prophylactic therapy (or vice versa) based on the perceived burden, their activity level, and their overall health status.

The terminology for prophylaxis was revised in the 2012 World Federation of Hemophilia guideline to clarify whether prophylaxis is primary (before a bleeding event has occurred) or secondary, and continuous or intermittent (eg, for a few months at a time) (table 2).

- **Primary prophylaxis** – Individuals who have not had a bleeding episode but are at high risk of bleeding based on severe factor deficiency (eg, factor VIII or factor IX activity level <1 percent) are recommended to receive primary prophylaxis due to the high risk of spontaneous bleeding and efficacy of prophylaxis in preventing bleeding and its complications [24]. Primary prophylaxis has been used extensively in parts of Europe, particularly in Sweden, and has been accepted by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) and the Pediatric Working Party of the United Kingdom Haemophilia Doctors' Organisation (UKHDO) as the optimal treatment modality for patients with severe hemophilia [29-31].

- **Secondary prophylaxis** – For individuals who have had more than one bleeding episode (eg, two or more bleeds into a target joint, evidence of joint disease by physical examination or radiography), secondary prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level. Those with severe disease (factor activity <1 percent) and more than one bleeding episode should receive secondary prophylaxis, whereas those with moderate or mild disease (factor activity 5 to 40 percent) and more than one bleeding episode may be able to use intermittent prophylaxis.

- **Intermittent prophylaxis** – For individuals with moderate or mild factor deficiency (factor VIII or factor IX activity level >5 percent) and no prior bleeding, the need for prophylaxis is individualized based on the patient's factor level, which factor is deficient (factor VIII or factor IX), and the patient's physical activity level. Intermittent prophylaxis (also called "short-term prophylaxis"), which is administered for several weeks to months and then discontinued, may be used in specific circumstances such as high-impact physical activities, joint bleeding, or surgical procedures. We are more likely to use prophylaxis in those with lower baseline factor levels (closer to 5 percent) and in those with moderate factor VIII deficiency than those with moderate factor IX deficiency, but the individual bleeding phenotype must be considered in decision-making.

Many individuals for whom prophylaxis is appropriate may not have access to factor infusions due to high costs and/or lack of resources. In resource-limited settings, options for those who cannot receive regular prophylaxis include intermittent prophylaxis and/or prophylaxis using lower doses. As an example, a 2016 study from India of patients with factor VIII deficiency found that prophylaxis using factor VIII at 10 units/kg (rather than the usual 25 to 40 units/kg) twice per week was cost-effective and significantly reduced joint bleeds and school absenteeism [32].

Evidence for the benefit of prophylaxis in reducing morbidity comes from randomized trials and observational studies, as well as experience with individuals who have factor activity levels above 1 to 2 percent and have significantly lower bleeding rates than those with factor levels <1 percent [1]:

- A 2007 trial randomly assigned 65 boys with hemophilia A (factor VIII activity <2 percent) who were under 30 months of age to receive prophylaxis with recombinant factor VIII (25 units/kg every other day) or episodic therapy only at the time of joint bleeding [33]. At six years of age, imaging studies of the ankles, knees, and elbows using magnetic resonance imaging (MRI) was performed. This showed a greater protection from joint damage (all six joints normal) in those assigned to prophylaxis (25 of 27 boys [93 percent]) compared with those assigned to episodic treatment (16 of 29 [55 percent]), with a relative risk (RR) of joint damage with episodic therapy of 6.1 (95% CI 1.5-24.4). Total bleeding events (joints and other sites) were also significantly less in the prophylaxis group (mean, 3.3 versus 17.7 per person per year). Adverse events included development of a factor VIII inhibitor in two boys in the prophylaxis arm (6 percent) and life-threatening hemorrhage in three boys in the episodic therapy group (9 percent).

- A 2011 trial (Evaluation Study on Prophylaxis: a Randomized Italian Trial [ESPRIT]) randomly assigned 45 children with severe hemophilia A (factor VIII activity <1 percent)

who were one to seven years of age (median age, four years) to receive prophylaxis with recombinant factor VIII (25 units/kg three times per week) or episodic therapy at the time of bleeding [34]. After a median period of approximately seven years of observation, joint bleeding was assessed by standard radiography. This showed a lower number of hemarthroses with regular prophylaxis than with episodic treatment (mean number of hemarthroses per patient 14.7 versus 40). Total bleeding events were significantly less in the prophylaxis arm (mean 38 versus 82 over the entire study period). Joint preservation was especially good in those who started prophylaxis at the age of three years or younger; none of the eight patients who began prophylaxis by age three had joint damage, compared with 3 of 10 (30 percent) of children of the same age assigned to episodic therapy.

- Trials in adults who were previously receiving on-demand therapy and converted to prophylaxis have all noted reductions in bleeding episodes [35-39]. As an example, in a series of 20 adults who converted from an on-demand schedule to routine prophylaxis, joint bleeds decreased from approximately two to four bleeds per month to approximately 0 to 0.5 bleeds per month [36].

- Several observational studies have also found that routine prophylaxis was associated with a reduction in joint bleeding and chronic arthropathy, especially when started early and targeted to individuals with severe disease [26,40-42].

Choice of prophylactic therapy — Factor replacement products are available for hemophilia A and B. Individuals with hemophilia A also have the option of prophylactic emicizumab.

The choice of prophylactic therapy is multifaceted, even for hematologists, and decisions should be made in consultation with a hemophilia expert. All of the available prophylaxis products can produce satisfactory hemostasis. However, they have different patient responses, different safety profiles (risks of inhibitor development, burdens and costs), and different product characteristics (product half-life, effects on monitoring) [43].

We individualize the decision between factor replacement and emicizumab, and for those using factor replacement, we individualize the choice of replacement product, based on the patient's circumstances and needs, following an open discussion with the patient regarding data on specific products and patient values and preferences.

Once we determine which product is best for a patient, we make every effort to obtain this product, which may include providing the data and rationale to a third party payor.

- **Inhibitor development** – Inhibitor development (both low and high titer inhibitors) can greatly interfere with the ability to treat bleeding and achieve adequate hemostasis. High titer inhibitors bind to exogenously administered replacement factor and prevent it from achieving hemostasis. Inhibitor development is greatest in individuals with hemophilia A and those with severe deficiency, likely because it is the infused factor will be seen as a foreign protein in these individuals. Emicizumab is active in the presence of a factor VIII inhibitor since it lacks shared epitopes with factor VIII.

  Information on risks of inhibitor development with different types of therapies, factor concentrates and recombinant products is discussed in detail separately. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication", section on 'Therapy considerations'.)

- **Safety from viral infections** – Viral infections (eg, human immunodeficiency virus [HIV], hepatitis B and C viruses [HBV and HCV]) affected large numbers of people with hemophilia who received plasma-derived factor concentrates in the 1970s, 1980s, and early 1990s. Plasma-derived factor concentrates have been free of HIV, HBV, and HCV transmission since approximately 1993; however, concerns remain that potential transmission of blood borne diseases could occur, and this must be understood by patients and caregivers. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Infection from plasma-derived products'.)

  We often use a recombinant product made in a human cell line with tighter binding to von Willebrand factor. Ultrapure products are also preferred for individuals who are infected with HIV, as they stabilize the CD4 cell count [44].

  Emicizumab is a genetically engineered monoclonal antibody and is not associated with infectious risk.

- **Product half-life** – A number of recombinant factor products with modifications to extend their half-lives have been produced. These products have the advantage of decreasing the dosing frequency while maintaining adequate factor levels, especially for factor IX. These products are often more expensive per unit compared with other plasma-derived and recombinant products. Importantly, the decreased dosing frequency may reduce the need for a central venous catheter and the risk of catheter-associated complications in some patients. We often use these products for prophylaxis in children and individuals with factor IX deficiency who require prophylaxis.

  Details of available longer half-life products, their mechanisms of action, dosing, and efficacy are presented below. (See 'Longer lasting recombinant factor VIII' below and

'Longer-lasting recombinant factor IX' below.)

Emicizumab is given once per week for a loading dose, after which the dosing interval can be further tailored and/or extended to once every two weeks or once every four weeks. (See 'Emicizumab dosing' below.)

- **Cost** – Replacement products are expensive, especially longer lasting products. However, overall cost depends on how the product is used and the rate of breakthrough bleeding. Even the most expensive product may be cost-effective if it reduces the frequency of bleeding. Cost and third party coverage for factor products that takes into account the patient's clinical circumstances must be discussed. Countries and local institutions may have specific agreements in place that result in cost reductions. Enrollment in a clinical trial may also be an option for cost reduction [43].

All of the available clotting factor replacement products are administered intravenously, with the majority requiring reconstitution. Emicizumab is administered subcutaneously. (See 'Emicizumab for hemophilia A' below.)

Age of initiation and dosing schedule — The goal of prophylaxis is to reduce (or, ideally, prevent) bleeding. Thus, it is generally initiated at as young an age as reasonably possible. Dosing is scheduled to maintain sustained, protective factor levels. However, both age at initiation and dosing frequency need to be balanced against the risks and burdens of therapy that is administered intravenously. In many cases, prophylaxis implies the need for a central venous access device, which must be maintained and used properly, and carries risks of infection and thrombosis. These risks, types of devices, and their proper care and use, are presented separately. (See "Central venous access in adults: General principles" and "Central venous catheters: Overview of complications and prevention in adults" and "Routine care and maintenance of intravenous devices".)

- **Age** – For hemophilia A, the benefit of starting prophylaxis at as young an age as possible is balanced against the burdens of regular (two to three times per week) intravenous therapy in an infant (not a concern with emicizumab). We generally advise patients with severe hemophilia (factor activity level <1 percent) to start prophylaxis when they have significant bleeding such as a joint bleed or other bleeding that requires treatment with factor (but not for minor bruising or oral bleeding). This may be at approximately one year of age for some children and older for others. Some centers routinely start prophylaxis at 1 to 1.5 years of age [45]. Increasing use of emicizumab in hemophilia A alters the risk-benefit calculation because dosing is much less frequent and is administered subcutaneously. (See 'Emicizumab for hemophilia A' below.)

Another option for factor administration in patients or families/caregivers who place a higher value on avoiding or delaying factor infusions (or venous access device insertion) is to wait until it becomes clear whether the patient is going to have frequent bleeding episodes. This has the advantage of potentially avoiding factor infusions in patients with infrequent or no bleeding. However, there is a potential risk of life-threatening bleeding if prophylaxis is not given. Neither of these risks are predictable.

The benefits of starting prophylaxis at a young age or soon after the first joint bleed have been shown in several studies:

- In a 2017 analysis from a United States hemophilia treatment center surveillance registry that included over 6000 patients followed for approximately 12 years, normal joint mobility was preserved in those who started prophylaxis before age 4 years [46]. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Hemophilic arthropathy'.)

- In a 2002 study involving 76 patients who started prophylaxis at different ages and were followed for two decades, the risk of long-term joint damage increased by 8 percent for every year after the first joint bleed that prophylaxis was delayed [47]. The median age of first joint bleed in this study was 2.2 years, consistent with that seen in other studies. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Age at first bleeding'.)

- In a 1999 series of 121 patients who started prophylaxis at different ages, the frequency of developing arthropathy was less in those who started prophylaxis at age 0 to 2 years compared with those who started between ages 3 and 10 years [48]. The bleeding rate also decreased with shorter interval dosing (eg, less bleeding with dosing two times weekly [hemophilia B] or three time weekly [hemophilia A] compared with once weekly). In a subgroup of 55 patients who used a more intensive schedule (factor infusion three times weekly), there was no significant difference in bleeding rate between those who started prophylaxis before age 3 years or between 3 and 5 years.

Importantly, joint bleeding is not the only clinically important outcome. Studies to evaluate the benefit of prophylaxis in reducing other bleeding complications are ongoing.

- **Dosing schedule** – The goal of dosing has traditionally been to maintain the factor level above 1 to 2 percent, essentially converting the patient from a severe to a moderate hemophilia phenotype. However, an analysis of bleeding frequency determined that for every 1 percent increase in factor activity level there would be an 18 percent reduction in

bleeding frequency, suggesting that a trough level of 1 to 2 percent may not be adequate in some cases [49].

When determining a dosing interval, it should be noted that larger doses given less frequently will produce higher peaks; smaller doses given more frequently will provide more uniform factor levels but involve more venipuncture and handling of factor.

The dosing and monitoring schedule are highly dependent on the patient (patient-specific product half-life, values and preferences related to bleeding risk and burdens of more frequent dosing) and which factor is deficient. Very young children may be able to tolerate a lower trough level (eg, 1 to 2 percent) than older children who are more active and/or demonstrate a severe bleeding pattern. The dosing schedule can be adjusted according to the patient's trough factor level, bleeding rate, and intravenous access. The presence of a central venous access device facilitates more frequent monitoring of trough levels, but this may not be required in all patients.

The following are examples of typical starting schedules [13]:

- **Hemophilia A** – Factor VIII, 25 to 40 units/kg of body weight, given three times per week (Malmo protocol) or 15 to 30 units/kg three times per week (Utrecht protocol). If a longer lasting product is used, small children may start with once or twice per week dosing and work up to the optimal dosing and trough level.

  Other schedules such as every other day are also used; it is important to consult the product information for the specific product being administered, and the patient's individual pharmacokinetics.

  Dosing for emicizumab is discussed below. (See 'Emicizumab for hemophilia A' below.)

- **Hemophilia B** – Factor IX, 25 to 40 units/kg of body weight, given two times per week (Malmo protocol) or 15 to 30 units/kg two times per week (Utrecht protocol). Longer lasting products allow for once per week or once every two week dosing.

Management of product choice and dosing schedule is optimally done through a hemophilia treatment center. It is preferable to give the factor in the morning so that levels will be higher during periods of activity rather than during sleep. The vial size closest to the calculated dose should be used to limit the number of vials required.

For adults who have previously been receiving on-demand therapy and want to switch to prophylaxis, dosing is similar, although the typical amount of factor used during on-demand treatment and/or the circumstances in which bleeding was most likely to occur

can also be incorporated into the dosing schedule (eg, dosing immediately before activities that previously were associated with bleeding, termed "activity-based prophylaxis"). Some adults with factor VIII deficiency may start with once weekly prophylaxis, which will significantly decrease bleeding and can acclimate them to the use of prophylaxis.

Flexibility in dosing schedules is supported by a 2012 trial that randomly assigned 66 patients with hemophilia A to receive standard dosing (20 to 40 units/kg every other day) or adjusted dosing based on pharmacokinetic data (20 to 80 units/kg every third day) and found that the two arms were comparable in annualized bleeding rates, total factor usage, and adverse event rates [35].

The importance of an adequate trough factor activity level in reducing "breakthrough" bleeding was demonstrated in a study involving 143 children and adults with severe hemophilia A who were receiving routine prophylaxis [50]. The amount of time with trough factor VIII activity levels below 1, 2, and 5 percent were calculated from pharmacokinetic data and infusion records; this analysis showed that bleeding correlated strongly with lower trough levels, such that each hour spent with a factor VIII activity <1 percent was associated with a 2.2 percent increase in annualized bleeding rate.

Can prophylaxis be discontinued? — Once prophylaxis is started, a question may arise regarding whether or when the patient can or should be transitioned to on-demand treatment. The answer is highly patient-dependent, and we usually base our decisions on the symptoms being reported and the concerns of the patient. As an example, some adults may wish to switch to a less frequent regimen or have a trial off prophylaxis, with close observation of the effects on musculoskeletal symptoms and quality of life.

In a 2005 series that included 80 patients with severe hemophilia A or B who received prophylaxis during childhood, approximately one-third discontinued prophylaxis (median age of discontinuation, 21.5 years) [51]. At a median follow-up of 3.5 years, the individuals who stopped prophylaxis had a slightly higher rate of joint bleeds (3.2 versus 1.8 per year), but an equivalent clinical outcome based on clinical examination score that included inflammation, deformity, and instability; and a radiologic (Pettersson) score. However, these radiologic scores lag behind clinical bleeding events. We inform patients that the risk of development of joint disease continues when prophylaxis is discontinued, as does the risk of intracranial or other life-threatening bleeding events.

Available products — The tables list available factor products for factor VIII (table 3) and factor IX (table 4), which are described in the sections that follow. An updated table is also

maintained by the of the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) in the United States (www.hemophilia.org) [52,53].

Factor VIII products for hemophilia A — Products used to treat hemophilia A (inherited deficiency of factor VIII [factor 8]) include factor VIII replacement products (concentrates from plasma, recombinant products, and recombinant products with extended half-life) as well as emicizumab. Emicizumab is a humanized bispecific monoclonal antibody that binds to both factor IXa and factor X, substituting for the role of factor VIII in hemostasis, as described in more detail below.

Data from the HAVEN 3 trial, discussed below (see 'Emicizumab for hemophilia A' below), show that emicizumab has improved efficacy and reduced adverse effects compared with factor VIII products, making this an important option for all individuals with hemophilia who would benefit from prophylaxis, if available. Lack of insurance coverage for emicizumab may be a barrier for some patients.

Factor VIII products can be derived from processed human plasma or produced from cell lines engineered to express large amounts of factor VIII (also called genetically engineered or recombinant factor VIII).

Available factor VIII products and their characteristics are listed in the table (table 3); an updated table is also maintained by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) in the United States (www.hemophilia.org) [52,53].

Factor VIII concentrates from plasma — Plasma-derived factor VIII concentrates are prepared by commercial fractionation of carefully screened donor plasma. They are stratified based on purity; greater purity reflects a higher ratio of factor VIII to non-factor VIII proteins [54,55].

Viral inactivation procedures (pasteurization, solvent-detergent treatment, chemical disruption with sodium thiocyanate, or ultrafiltration) add another layer of protection against HIV and hepatitis viruses. Parvovirus B19, a non-lipid-enveloped virus, is an exception to elimination by heat inactivation and solvent/detergent methods, and parvovirus infection has been reported with a solvent/detergent treated, plasma-derived factor concentrate [56,57]. (See "Blood donor screening: Laboratory testing" and "Pathogen inactivation of blood products", section on 'Solvent/detergent treatment'.)

For the ultrahigh purity products, affinity chromatography using monoclonal antibodies provides an additional purification step [54]. Preparation of factor VIII from Cryoprecipitate is no longer done.

- **Intermediate purity** – These products typically contain 6 to 10 units of factor VIII/mg protein.

- **High purity** – These products contain at least 50 units of factor VIII/mg protein (range 50 to 150 units/mg protein), excluding albumin used for stabilization.

- **Ultrahigh purity** – These products are monoclonal antibody (mAb) affinity-purified and contain 3000 units of factor VIII/mg protein, excluding albumin used for stabilization [54,55]. This concentration is essentially identical to the purity of recombinant products [54,55].

Plasma-derived factor VIII concentrate products include Hemofil-M and Koate (previously called Koate DVI); Hemofil-M is monoclonal antibody-purified (ie, ultrahigh purity) and Koate is chromatography-purified (ie, high purity). Monoclate-P was discontinued in 2018.

Intermediate purity VWF/factor VIII concentrates (Humate-P, Alphanate, Wilate) contain factor VIII and von Willebrand factor (VWF) [58]. They are mainly used for the treatment of von Willebrand disease (VWD).

Products can also be classified by other properties such as half-life, as done in the table (table 3).

Recombinant human factor VIII — Recombinant factor VIII products include a number of genetically engineered proteins produced in either animal or human cell lines. For the most part, these are made using modified versions of the human factor VIII gene. They are characterized by "generation," which reflects decreasing exposure to animal proteins [54,55].

Available products are characterized by their "generation," which reflects the species of cell line in which they are produced and the addition of or exposure to human and/or animal protein in the final product:

- **First generation** – First generation recombinant human factor VIII (rFVIII) products (eg, Recombinate) are produced from the cell culture supernatant of transfected animal cell lines. These products also have been exposed to bovine albumin or human albumin as a stabilizer, conferring a theoretical risk of viral exposure [59,60].

- **Second generation** – Second generation rFVIII products (eg, Kogenate-FS, ReFacto) are produced from the cell culture supernatant of transfected animal cell lines, but they do not contain albumin in the final preparation. They are stabilized using sucrose [61-63].

- **Third generation** – Third generation rFVIII products (eg, Advate, Kovaltry, Novoeight, Xyntha) are produced in animal cell lines; they have no added human or animal protein [64,65]. Viral inactivation steps are also used.

- **Fourth generation** – Fourth generation rFVIII products (eg, Afstyla, Nuwiq), recombinant human factor VIII pegylated (eg, Adynovate), and recombinant human factor VIII Fc fusion protein (eg, Eloctate) are produced in human cell lines; they have no added human or animal protein. In principle, production in a human cell line could make the protein more similar to endogenous factor VIII.

Additional modifications of the factor VIII gene can be made to enhance production and/or improve the pharmacokinetic profile of the product (see "Biology and normal function of factor VIII and factor IX", section on 'Structure'). These modifications include the following:

- **B-domain deletion** – "B-domain deleted" products have a genetic modification to remove part of the factor VIII gene; this improves production efficiency but does not alter the function of the protein. Examples include Xyntha, Novoeight, Nuwiq, and Eloctate. The portion of factor VIII encoded by the B-domain of the gene is not required for clotting activity [62,66]. B-domain deletion confers greater stability on the resultant smaller factor VIII molecule.

- **Single chain** – "Single chain" products have a genetic modification that creates a single molecule in which the heavy and light chains of factor VIII are fused, resulting in production of a single protein. This is intended to confer increased stability of the resultant factor VIII molecule [67]. However, for the most part, single chain products have similar half-lives to other recombinant, standard half-life products. Nuwiq may have a slightly longer half-life in some adults, which is hypothesized to be related to tighter binding to VWF.

All of these products have been demonstrated to have excellent efficacy and safety profiles in clinical studies in which they reliably treated or reduced bleeding episodes [54,55,68-71]. Different recombinant products (or different generation products) have not been directly compared in randomized trials, with the exception of the SIPPET trial, which compared recombinant to plasma-derived products containing VWF. This trial is discussed in detail separately. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication", section on 'Therapy considerations'.)

Additional recombinant products have been produced in which other molecules are added to factor VIII to extend its half-life. (See 'Longer lasting recombinant factor VIII' below.)

Longer lasting recombinant factor VIII — Factor VIII preparations with longer half-lives have the advantage of less-frequent dosing, enhancing the ease of administration for some patients.

Decisions to use a longer half-life product are individualized and balanced based upon the cost and benefit for each patient. For some patients, a modest decrease in the number of infusions may result in increased cost. In contrast, for some small children, a decrease in the frequency of infusion may allow avoidance of a central venous access device. Older individuals who use on-demand dosing of factor VIII may also benefit from weekly prophylaxis using a longer half-life product.

Approved products are listed below. Additional factor VIII modifications designed to improve potency, stability, and other pharmacokinetic parameters are in development. (See "Gene therapy and other investigational approaches for hemophilia" and "Gene therapy and other investigational approaches for hemophilia", section on 'Half-life extension'.)

Efanesoctocog alfa (factor VIII-VWF fusion) — Efanesoctocog alfa (Altuviiio; previously called BIVV001 or rFVIIIFc-VWF-XTEN) is a recombinant factor VIII molecule that was approved by the US Food and Drug Administration (FDA) in February 2023 for children and adults with hemophilia A [72].

This molecule circumvents factor VIII dependence on VWF for stability. It does so by fusing B domain-deleted factor VIII to the VWF D'D3-domain (the factor VIII binding site), along with Fc and two XTEN polypeptides, which further increase stability (figure 1) [73,74]. The resulting half-life extension confers the ability to decrease the frequency of administration to once weekly for prophylaxis and can provide protective factor VIII activity levels for several days if given to treat bleeding.

A 2023 study administered once-weekly efanesoctocog alfa (50 units/kg) to 133 individuals ≥12 years of age with factor VIII levels <1 percent and at least 150 previous exposure days [75]. The median annualized bleeding rate with once-weekly prophylaxis was 0 (interquartile range, 0 to 1.04), and the mean annualized bleeding rate was 0.71 (95% CI 0.52-0.97). An additional 26 individuals were treated with on-demand efanesoctocog alfa for bleeding during a period of 26 weeks, followed by 26 weeks of once-weekly prophylactic therapy. In these individuals, the annualized bleeding rate on prophylaxis decreased from 17 to 0. The mean factor VIII activity was >40 percent for the majority of the week, with a nadir of 15 percent on the seventh day. Therapy was well tolerated, and the mean half-life was 47 hours.

An earlier dose-finding and pharmacokinetic study determined that after one dose of 65 international unit, half-life was approximately 43 hours and the factor level after seven days was

17 percent, supporting the once-weekly administration schedule [76].

No inhibitors developed in either study [76].

Factor VIII-Fc fusion — A recombinant product composed of factor VIII fused with a monomeric human immunoglobulin (IgG1) Fc domain (rFVIII-Fc; Eloctate) was approved by the US Food and Drug Administration (FDA) in 2014 for treatment of bleeding, prevention of bleeding, and perioperative management of patients with hemophilia A [77]. This product binds to the neonatal Fc receptor (FcRn, present on many adult cell types) via its Fc domain, and this binding protects the factor from degradation, extending the half-life of factor VIII 1.5- to 1.7-fold.

In an open label pilot study (16 patients) and a subsequent dosing study (165 patients), this product was well-tolerated and patients did not develop antibodies or inhibitors to the fusion protein during 28 days of observation and 50 exposure days, respectively [78,79]. Compared with recombinant factor VIII lacking the Fc fusion, rFVIII-Fc had a longer therapeutic duration as judged by several pharmacokinetic parameters. As an example, at the 65 international units/kg dose, the half-life of rFVIII was 11 hours, compared with 18.8 hours for the rFVIII-Fc, a 1.7-fold improvement [78]. Twice weekly prophylactic dosing resulted in trough factor VIII levels of at least 1 to 3 units/dL in most patients [79]. Pharmacokinetic studies have reported a shorter half-life in children younger than six years compared with adults; however, dosing in all patients is based on trough levels and bleeding symptoms rather than strictly calculated half-lives. Of note, there is wide variation in the pharmacokinetics of factor VIII among different individuals.

Factor VIII-PEGylated — A recombinant product composed of factor VIII covalently fused to one or more polyethylene glycol (PEG) molecules (pegylated rFVIII; Adynovate) was approved by the FDA in 2015 for the treatment and prevention of bleeding in individuals 12 years of age and older with hemophilia A, which was expanded in 2016 to include children <12 years [80,81]. The PEG molecules extend the half-life by 1.4- to 1.5-fold [82]. Studies in the setting of on-demand therapy or surgery have shown this product to be safe and hemostatically effective [82,83]. A glycoPEGylated product (Esperoct) was approved in 2019 [84]. PEGylation and glycoPEGylaton differ in the site to which the PEG moiety is added (amino group of the protein versus carbohydrate, respectively) [85].

An earlier product in which factor VIII was reconstituted in PEGylated liposomes was not pursued due to similar pharmacokinetics with other standard half-life factor VIII products.

Single chain factor VIII — Single chain products may have a slightly increased half-life, although the prolongation is not as great as with the other modifications discussed in this section. (See 'Recombinant human factor VIII' above.)

Recombinant porcine factor VIII — A recombinant, B domain-deleted porcine (pig) factor VIII (rpFVIII; Obizur) is available for treating patients with autoantibodies to factor VIII (ie, patients with an acquired factor VIII inhibitor). This product is not licensed for use in patients with inherited hemophilia A. In principle, it is effective for individuals with hemophilia A who have an inhibitor and serious bleeding, and whose porcine factor VIII inhibitor titer is low enough to allow a hemostatic porcine factor VIII level. The cross-reactivity of antibodies against human factor VIII with porcine factor VIII is approximately 30 to 50 percent [86]. (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)", section on 'Management' and "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'Inhibitors'.)

A plasma-derived porcine factor VIII product manufactured from pigs (rather than the porcine DNA sequence) is no longer available.

Emicizumab for hemophilia A

Overview of emicizumab — Emicizumab-kxwh (Hemlibra, emicizumab, previously designated ACE910) is a recombinant humanized bispecific monoclonal antibody that binds to factors IXa and X simultaneously, bringing these two molecules together and essentially substituting for the scaffold role of factor VIIIa as a cofactor for factor IXa in activating factor X, as illustrated in the graphic (figure 2) [87-89]. Emicizumab was approved by the US Food and Drug Administration (FDA) for individuals with hemophilia A with inhibitors in late 2017 and for those without inhibitors in late 2018 [90,91]. The "kxwh" is a four-letter suffix designated by the FDA to help in distinguishing related biologic products; the letters have no meaning [92].

Emicizumab is an option for prophylaxis in individuals with hemophilia A with or without inhibitors, following a discussion of the potential risks and benefits compared with other approaches such as factor replacement or on-demand therapy for individuals without inhibitors, or immune tolerance induction (ITI) or on-demand treatment with a bypassing agent (eg, factor eight inhibitor bypassing activity [FEIBA] or recombinant activated factor VII [rFVIIa]) for individuals with inhibitors.

Emicizumab lowers bleeding rate in individuals with inhibitors. Therapy is started with a loading dose of 3 mg/kg subcutaneously once weekly for four weeks. Subsequent maintenance dosing can be done using 1.5 mg/kg subcutaneously once per week, 3 mg/kg subcutaneously once every two weeks, or 6 mg/kg subcutaneously once every four weeks. The subcutaneous administration route increases the ease of use.

Emicizumab is not effective for acute bleeding. (See "Acute treatment of bleeding and surgery in hemophilia A and B".)

Use of emicizumab requires knowledge regarding the treatment of breakthrough bleeds and/or prior to invasive procedures (eg, need for a bypassing agent for people with inhibitors or use and monitoring of factor VIII replacement products for people without inhibitors), as well as the necessary monitoring based on the treatment administered and the patient's symptoms. Standard aPTT-based coagulation tests and factor VIII activity assays are affected by emicizumab and cannot be used to monitor efficacy. If an individual receiving emicizumab prophylaxis requires factor VIII infusions, the factor VIII activity and inhibitor titers must be measured using a bovine substrate-based chromogenic assay (bovine chromogenic factor VIII activity assay) [93].

Individuals receiving emicizumab should be aware of a Boxed Warning regarding the development of unusual thrombotic events and thrombotic microangiopathy (TMA); these were seen in the trial involving individuals with inhibitors who were receiving a bypassing agent. Trials in individuals without inhibitors did not observe these complications. Avoidance of co-administration with an activated prothrombin complex concentrate (aPCC; eg, FEIBA) at a dose above 100 units/kg total dose for one day or longer reduces this risk. If thrombotic events occur during co-administration, the aPCC should be discontinued. (See "Drug-induced thrombotic microangiopathy (DITMA)", section on 'Emicizumab'.)

Emicizumab efficacy and adverse events — In clinical trials, prophylaxis with emicizumab significantly reduced the annualized rate of bleeding events experienced by factor VIII-deficient patients with inhibitors as well as those without inhibitors:

- **Prophylaxis in patients with an inhibitor** – Emicizumab was tested as prophylaxis in individuals with hemophilia A and inhibitors (109 individuals ages 12 years or older in the HAVEN 1 trial and 85 children age 2 to 11 years along with three older adolescents in the HAVEN 2 trial) [94,95].

  - **Age ≥12 years** – Participants in HAVEN 1 were randomly assigned to once-weekly subcutaneous emicizumab or standard therapy without bypassing prophylaxis for 24 weeks, after which they could continue therapy at the same or increased dose of emicizumab if they experienced breakthrough bleeding [94]. Compared with controls, emicizumab-treated patients had a reduction in annualized bleeding rate (23.3 versus 2.9 events) as well as improvements in other measures of bleeding such as rates of bleeding in specific sites or complete absence of bleeding during the study (63 versus 6 percent). In patients who had previously been receiving a bypassing agent, emicizumab reduced bleeding more effectively (annualized bleeding rate, 15.7 versus 3.3 events). Adverse events were mostly injection-site reactions, although three patients who were receiving an aPCC along with emicizumab had a thrombotic microangiopathy (TMA),

one had a cavernous sinus thrombosis, and one had skin necrosis; these resolved with discontinuation of the aPCC.

- **Age 2 to 11 years** – Participants in HAVEN 2 were randomly assigned to one of three dose levels (1.5 mg/kg weekly, 3 mg/kg every two weeks, or 6 mg/kg every four weeks) for 52 weeks [95]. The overall annualized bleeding rate was 0.3 (95% CI 0.17-0.50); this represented a large improvement for those who were previously receiving a bypassing agent, who had an annualized bleeding rate of 21.1 (95% CI 15.99-27.82). Target joint bleeding improved as well; for the 34 with target joints, there was diminished bleeding in the joint during the first half of the study and no bleeding during the second half. Many had their central venous access device removed. One child developed an antibody of possible neutralizing potential, and there were no instances of TMA or thromboembolism.

- **Prophylaxis in patients without an inhibitor** – Emicizumab was tested as prophylaxis in 152 individuals ages 12 years or older with severe hemophilia A (factor VIII activity <1 percent) who did not have an inhibitor, most of whom were only receiving episodic therapy for bleeding (the HAVEN 3 trial, published in 2018) [96]. Participants were randomly assigned to prophylaxis with subcutaneous emicizumab at one of two dosing protocols or to no emicizumab. Compared with controls receiving only episodic therapy with factor VIII, individuals assigned to emicizumab prophylaxis had a dramatically reduced annualized bleeding rate (38 events versus 1.5 and 1.3 events at the two dosing protocols [1.5 mg/kg once weekly or 3 mg/kg every other week, respectively; in both cases an initial emicizumab "loading" dose of 3 mg/kg weekly for four weeks was administered]). All controls had at least one bleeding event during the study (24 weeks), whereas more than one-half of participants in both emicizumab groups had no bleeding events during the study. In the group of 48 patients who had been receiving routine factor VIII prophylaxis, transition to emicizumab reduced the annualized bleeding rate by 68 percent. Therapy was well-tolerated with no cases of TMA or thrombosis.

- **Bleeding despite factor prophylaxis** – Emicizumab was tested in an open-label study involving 18 individuals with severe hemophilia A who had bleeding episodes despite use of factor VIII prophylaxis, on-demand therapy, or bypassing therapy (in the 11 individuals with a factor VIII inhibitor) [97]. Patients were treated for 12 weeks in three cohorts of weekly administration, at dose levels that were estimated to provide an equivalent trough factor VIII level roughly equivalent to 3, 10, and 30 units/dL of factor VIII activity. Bleeding was remarkably decreased in 17 evaluable individuals, from a median annualized bleeding rate of 33 to a rate of 4 in the first cohort, from 18 to 0 in the second cohort, and from 15

to 0 in the third cohort. There were no serious adverse events, no thromboembolic complications, and no new anti-emicizumab antibodies. One patient stopped therapy early due to injection-site erythema, and one patient had a pre-existing antibody that reacted with emicizumab but did not interfere with the efficacy of the therapy.

Emicizumab dosing — Emicizumab is administered subcutaneously and has a long half-life (four to five weeks) [96,98].

All patients require a loading dose (3 mg/kg subcutaneously once per week for the first four weeks) [99]. After the loading dose, there are several dosing options, all of which begin one week after completing the loading dose:

- 1.5 mg/kg once per week
- 3 mg/kg once every two weeks
- 6 mg/kg once every four weeks

These dosing regimens appeared to have similar efficacy in clinical trials [94,96].

There is no routine monitoring of coagulation status with emicizumab. A 2019 guideline from the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) states that routine measurement of the drug is not necessary, but measurement of drug level is recommended in patients with suspected anti-drug antibodies (inhibitors of emicizumab), as evidenced by breakthrough bleeding, similar to that seen without treatment [100]. The aPTT can also be measured; if the aPTT is prolonged, emicizumab is not present/not working effectively.

Emicizumab effect on laboratory tests — Emicizumab affects the results of some laboratory testing [100]:

- Decreases (shortens) the aPTT.
- Affects aPTT-related assays including factor VIII activity.
- Interferes with chromogenic factor VIII activity assays that use human-derived factor IXa and FX (falsely increases results).
- Interferes with the standard inhibitor assay (cannot be performed).

These effects can persist for up to six months after discontinuation of emicizumab due to the long half-life [100].

The prothrombin time (PT) and thrombin time (TT) and tests based on these assays are generally unaffected. Anti-factor Xa-based chromogenic assays and immunogenic assays are also unaffected.

The best way to measure factor VIII activity (if needed) in a patient on emicizumab is to use a chromogenic assay with bovine factor IXa and X components. For individuals who require factor VIII replacement to treat breakthrough bleeding or require major surgery, a bovine chromogenic factor VIII assay without human factor reagents must be used. (See "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'Patients with hemophilia A receiving emicizumab'.)

Products for hemophilia B — Factor IX products are used to treat hemophilia B (inherited deficiency of factor IX [factor 9]). Previously used sources of factor IX such as prothrombin complex concentrates (PCCs) are not considered first-line therapy for hemophilia B due to an increased risk of thrombosis as well as risks of plasma exposure. Available products are listed in the table (table 4). An updated table is also maintained by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) in the United States (www.hemophilia.org) [52,53].

Plasma-derived factor IX — Plasma-derived factor IX concentrate products (eg, AlphaNine) are prepared by commercial fractionation (chromatography, monoclonal antibody affinity) of carefully screened donor plasma [101]. Viral inactivation procedures (pasteurization, solvent/detergent treatment, chemical disruption with sodium thiocyanate, or ultrafiltration) add another layer of protection against HIV and hepatitis viruses. (See "Blood donor screening: Laboratory testing" and "Pathogen inactivation of blood products", section on 'Solvent/detergent treatment'.)

These products provide excellent efficacy [101,102]. The product produced by chromatographic partitioning (AlphaNine) contains minor residual plasma proteins, whereas the monoclonal product (Mononine) is free of other plasma proteins. Viral attenuation to remove HIV and hepatitis is effective for both processes.

Recombinant factor IX — Recombinant human factor IX (eg, BeneFIX, Ixinity, Rixubis) has been genetically engineered by insertion of the human factor IX gene into a Chinese hamster ovary cell line. These products have been demonstrated to be safe and effective in the treatment of previously treated and previously untreated patients with hemophilia B [103-106]. The half-life of these products is 16 to 17 hours [102,107].

These products have no added albumin, giving them a theoretical safety advantage over plasma-derived concentrates [108]. The volume of distribution of recombinant factor IX is larger than that for plasma-derived factor IX, with a more pronounced increase in infants and children; as a result, a greater of number of units are needed compared with plasma-derived factor IX to

achieve the same factor activity level [109-111]. (See "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'Elective surgery'.)

Longer-lasting recombinant factor IX — Factor IX preparations with longer half-lives are available and confer a substantial prolongation of half-life, such that once weekly or every other week administration may be feasible.

The following strategies have been used for half-life extension for factor IX:

- **Recombinant factor IX-Fc fusion** – A recombinant product composed of factor IX fused with a monomeric human immunoglobulin Fc domain (FIX-Fc; Alprolix) was approved by the FDA in 2014 for prophylaxis and treatment of bleeding in individuals with hemophilia B, in both the routine and perioperative settings [112,113]. Approval for pediatric use was added in 2017 [114]. This product binds to the neonatal Fc receptor (FcRn, present on many adult cell types) via its Fc domain, and this binding protects rFIX-Fc from degradation, extending the half-life three- to fivefold compared with unmodified factor IX (eg, half-life of 54 to 90 hours, compared with 18 hours for native factor IX) [115,116].

  - **Adults** – In a study involving 123 previously treated patients with hemophilia B (age ≥12 years) who received once weekly prophylaxis (dose, 50 units/kg) or interval-adjusted prophylaxis (100 units/kg every 10 days, adjusted as needed), annualized bleeding rates were significantly lower than those for patients receiving on-demand therapy (3, 1.4, and 17.7, respectively) [117]. Individuals who had previously received episodic treatment were able to substantially decrease their bleeding rates with weekly to every other week prophylactic dosing. In two additional open label studies involving 138 patients with severe hemophilia B, there were no instances of inhibitor formation, thrombosis, or anaphylactic reactions with this product [116,117].

  - **Children** – In a study involving 30 previously treated boys with hemophilia B younger than 12 years who received once-weekly prophylaxis at a dose of 50 to 60 units/kg (interval and dose adjusted as needed), the median annualized bleeding rate was two for all bleeds and zero for joint bleeds [118]. The therapy was well-tolerated and no inhibitors developed during approximately six months of observation. The median dose based on pharmacokinetic studies was 59 units/kg once per week.

- **Recombinant factor IX-albumin fusion** – A recombinant factor IX product composed of the factor IX gene fused to the gene for albumin via a cleavable linker sequence (rFIX-FP; Idelvion) was approved by the FDA in 2016 for prophylaxis or treatment of bleeding in individuals with hemophilia B, both in the routine and perioperative settings [119,120]. The protein circulates as a fusion protein, and the linker is cleaved upon factor IX

activation, releasing activated factor IX (factor IXa). The half-life of this product is approximately 102 hours (approximately 5.6-fold prolongation) [120-122]. In addition to its efficacy in treating and preventing bleeding, this product also has the potential for higher trough levels, which may provide increased protection [120].

- **Glyco-PEGylated recombinant factor IX** – A recombinant factor IX product composed of factor IX with site-directed addition of polyethylene glycol (PEG) to the activation sequence of the factor IX protein (rFIX-GP; Rebinyn; previously called nonacog beta pegol [N9-GP]) was licensed in 2017 [123,124]. The PEG moiety is removed during factor IX activation [124]. The half-life of this product is approximately 93 hours (approximately fivefold prolongation) [125].

  In a study involving 74 patients with hemophilia B, annualized bleeding rates for individuals who received once weekly prophylaxis (dose, 40 units/kg or 10 units/kg) were significantly lower than that for patients receiving on-demand therapy (1.0, 2.9, and 15.6, respectively) [126]. A fair number of patients receiving prophylaxis had no bleeding events (67 percent of those receiving 40 units/kg, and 8 percent of those receiving 10 units/kg). There were no inhibitors or other safety concerns during one year of therapy.

PROPHYLACTIC THERAPIES UNDER DEVELOPMENT

A number of additional approaches to reduce the risk of bleeding in people with hemophilia are under various stages of conceptualization or development, including gene therapy for hemophilia A and hemophilia B. These approaches are discussed separately. (See "Gene therapy and other investigational approaches for hemophilia".)

RECOMMENDATIONS OF OTHERS

Guidelines for the management of hemophilia are published by the World Federation of Hemophilia and the National Hemophilia Foundation:

- **World Federation of Hemophilia (WFH)** guidelines were published in 2020 – WFH 2020 guidelines
- **Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF)** provides recommendations on various subjects – MASAC documents

These are largely consistent with the recommendations in UpToDate.

Links to additional hemophilia guidelines from other societies as well as links to guidelines related to other bleeding disorders are also available. (See 'Society guideline links' below.)

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

- **Comprehensive care** – Comprehensive health care is crucial for people with hemophilia because it minimizes other health risks that have the potential to become more serious due to an increased bleeding risk. Designated hemophilia treatment centers (HTCs) have been established in many parts of the world and provide integrated multidisciplinary care, and their involvement is demonstrated to reduce morbidity. United States HTCs are listed by the Centers for disease Control and Prevention. International HTCs are listed by the World Federation of Hemophilia. (See 'Routine/comprehensive care' above.)

    - Routine procedures (eg, heel stick, vitamin K administration, neonatal immunizations) should be performed by experienced personnel. Procedures such as circumcision

should be deferred until a hemophilia diagnosis is confirmed or excluded. (See 'Newborn care' above and 'Immunizations' above.)

- Appropriate oral hygiene and regular dental care is essential. An appropriate exercise regimen should be encouraged for maintenance of a healthy weight, cardiovascular risk reduction, and positive effects on strength, flexibility, balance, joint stabilization, bone density, socialization, and psychological health. Medicines that increase the risk of bleeding should be avoided. (See 'Dental care' above and 'Exercise and athletic participation' above and 'Medicines to avoid' above.)

- Advance detailed planning is required for invasive procedures, pregnancy, and travel. (See 'Planning for invasive procedures' above and 'Obstetric care and preconception counseling' above and 'Travel' above.)

- **Prophylaxis versus on-demand therapy** – Prophylactic therapy is highly effective in reducing bleeding and long-term complications; however, the costs and burdens remain high. Individuals at high risk of bleeding should receive primary prophylaxis (table 2). Secondary prophylaxis may be appropriate for those who have had more than one bleeding episode. For individuals with moderate or mild hemophilia and no prior bleeding, prophylaxis is individualized. Intermittent (short term, episodic) prophylaxis may be used in circumstances such as high-impact physical activities, joint bleeding, or surgical procedures. (See 'Prophylaxis versus on-demand therapy' above.)

- **Choice of product** – A large number of products are available for prophylaxis that can produce satisfactory hemostasis, including emicizumab for hemophilia A (figure 2) and numerous factor products for hemophilia A (table 3) and hemophilia B (table 4). Emicizumab has greater efficacy in reducing the annualized bleeding rate and greater ease of administration (subcutaneous dosing once weekly or every other week). The choice among products is individualized and takes into account safety, purity, risk of inhibitor development, half-life, individual pharmacokinetics, and cost. We make every effort to obtain the best product for each patient, which may include providing the data and rationale to a third party payor. (See 'Choice of prophylactic therapy' above and 'Available products' above.)

- **When to start** – For patients with severe hemophilia, we advise starting prophylaxis either prior to or when there is significant bleeding, which may be at around age one year for some children and older for others. Dosing is scheduled to maintain sustained, protective factor levels (eg, above 1 to 2 percent). Typical dosing schedules are listed above. (See 'Age of initiation and dosing schedule' above.)

- **Investigational therapies** – Gene therapy and other therapies under development are discussed separately. (See "Gene therapy and other investigational approaches for hemophilia".)

- **Hemophilia diagnosis and treatment of bleeding** – Separate topic reviews discuss hemophilia A and B diagnosis, treatment of bleeding, perioperative management, management of age-related morbidities, inhibitor eradication, and genetics. (See "Clinical manifestations and diagnosis of hemophilia" and "Acute treatment of bleeding and surgery in hemophilia A and B" and "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication" and "Genetics of hemophilia A and B".)

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Topic 107911 Version 51.0

GRAPHICS

Selected sports in hemophilia, high and low impact

Low impact sports	Moderate impact sports	High impact sports
Aquatics	Aerobics	BMX racing
Fishing	Basketball	Boxing
Frisbee	Horseback riding	Football (American)
Golf	Racquetball or tennis	Lacrosse
Hiking	Running/jogging	Rodeo
Walking	Soccer (world football)	Rugby

This table includes selected examples and should not take the place of clinician judgment regarding sports that are likely to cause injury or bleeding in individual patients. Refer to UpToDate for more information about hemophilia and sports participation.

BMX: bicycle motocross, a type of off-road sport cycling and stunt riding.

Reference:

1. *https://www.hemophilia.org/sites/default/files/document/files/Playing-It-Safe.pdf.*

Graphic 109841 Version 2.0

Types of prophylaxis for patients with hemophilia A or B

Type of treatment	Definition
Episodic (on demand) treatment	Replacement factor given at the time of bleeding
Continuous (regular) prophylaxis	Replacement factor given to prevent bleeding for at least 45 of 52 weeks (85%) of a year
▪ Primary prophylaxis	Continuous prophylaxis started before age three years and before the second large joint bleed
▪ Secondary prophylaxis	Continuous prophylaxis started after two or more large joint bleeds but before the onset of chronic arthropathy
▪ Tertiary prophylaxis	Continuous prophylaxis started after the onset of arthropathy to prevent further damage
Intermittent (periodic) prophylaxis	Replacement factor given to prevent bleeding for short periods of time such as during and after surgery

Replacement factor includes plasma-derived or recombinant factor concentrates. Refer to UpToDate for indications and details of factor administration and additional therapies for patients with hemophilia.

Adapted from:

1. *Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia 2013; 19:e1.*
2. *Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: Communication from the SSC of the ISTH. J Thromb Haemost 2014; 12:1935.*

Graphic 109728 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.

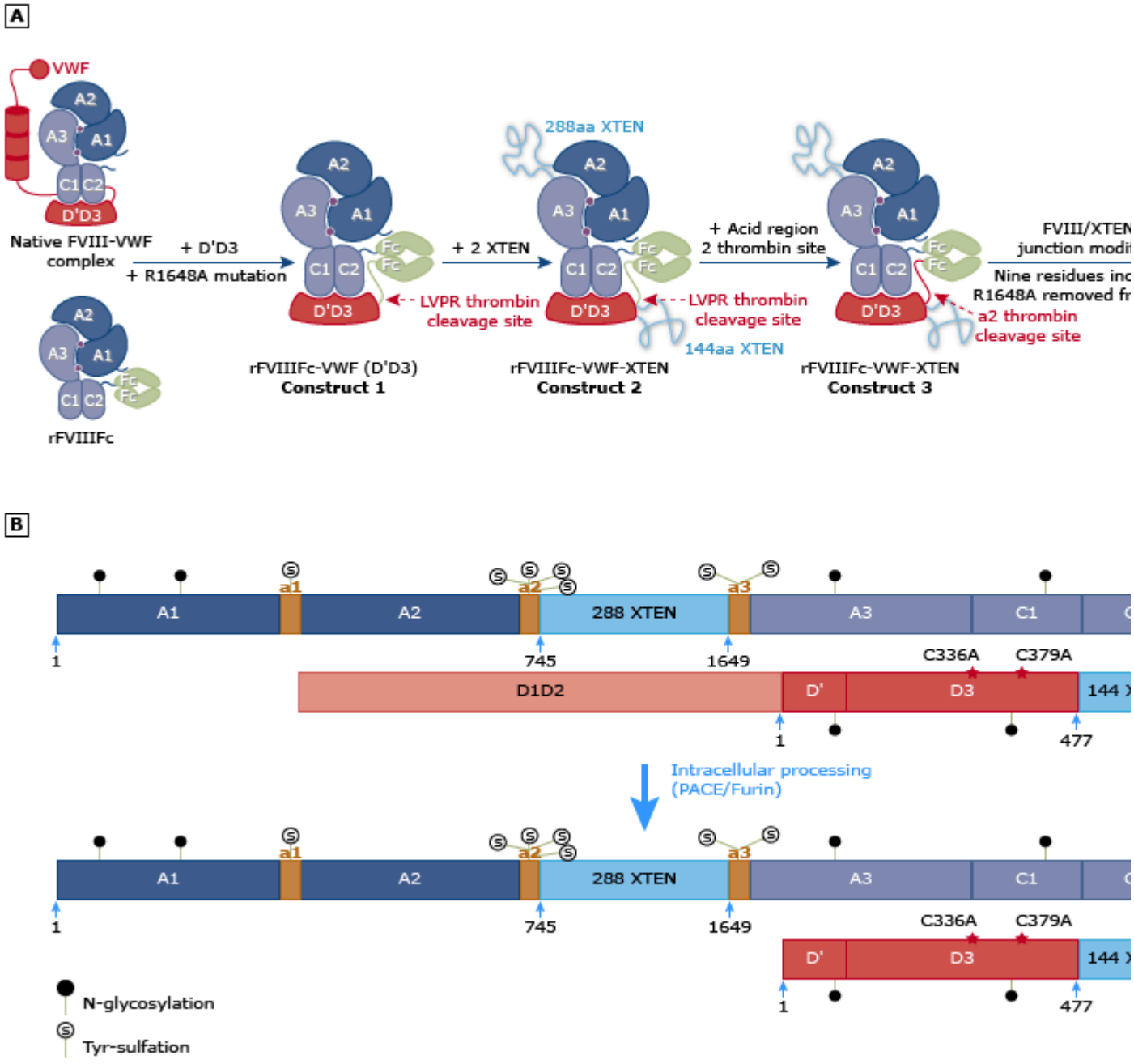
* Half-lives are **approximate**. Half-lives are generally shorter for children than adults when assessed in pharmacokinetic studies. The half-life of factor IX products without modifications to extend half-life is considered to be approximately 24 hours. The half-life should be determined for the individual 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

Development of rVIIIFc-VWF-XTEN (BIVV001)



rVIIIFc-VWF-XTEN uses several modifications of the human factor VIII molecule to extend its half-life.

(A) Stages in the synthesis of the new molecule. Construct 1 covalently attaches a D1D2D'D3 (C1099A/C1142A) domain of VWF through immunoglobulin-G1 Fc molecules, which prevents interaction of rFVIIIFc with endogenous full-length VWF. A R1648A mutation in FVIII prevents FVIII processing into heavy and light chains. Construct 2 inserts an XTEN polypeptide into the B-domain region of factor VIII and a shorter XTEN polypeptide between D'D3 and Fc. Construct 3 replaces the LVPR thrombin cleavage site with an FVIII acidic region 2 (a2) thrombin cleavage site. Construct 4 removes 3 amino acids from the factor VIII-XTEN junction and 9 amino acids from the B-domain linker to avoid potential MCH-Class II binding sites.

(B) Domain structure of the new molecule, which is generated in HEK293 cells. The two polypeptide chains are introduced separately and linked by disulfide bonds in the Fc region. During intracellular processing, several modifications occur including removal of the D1D2 propeptide.

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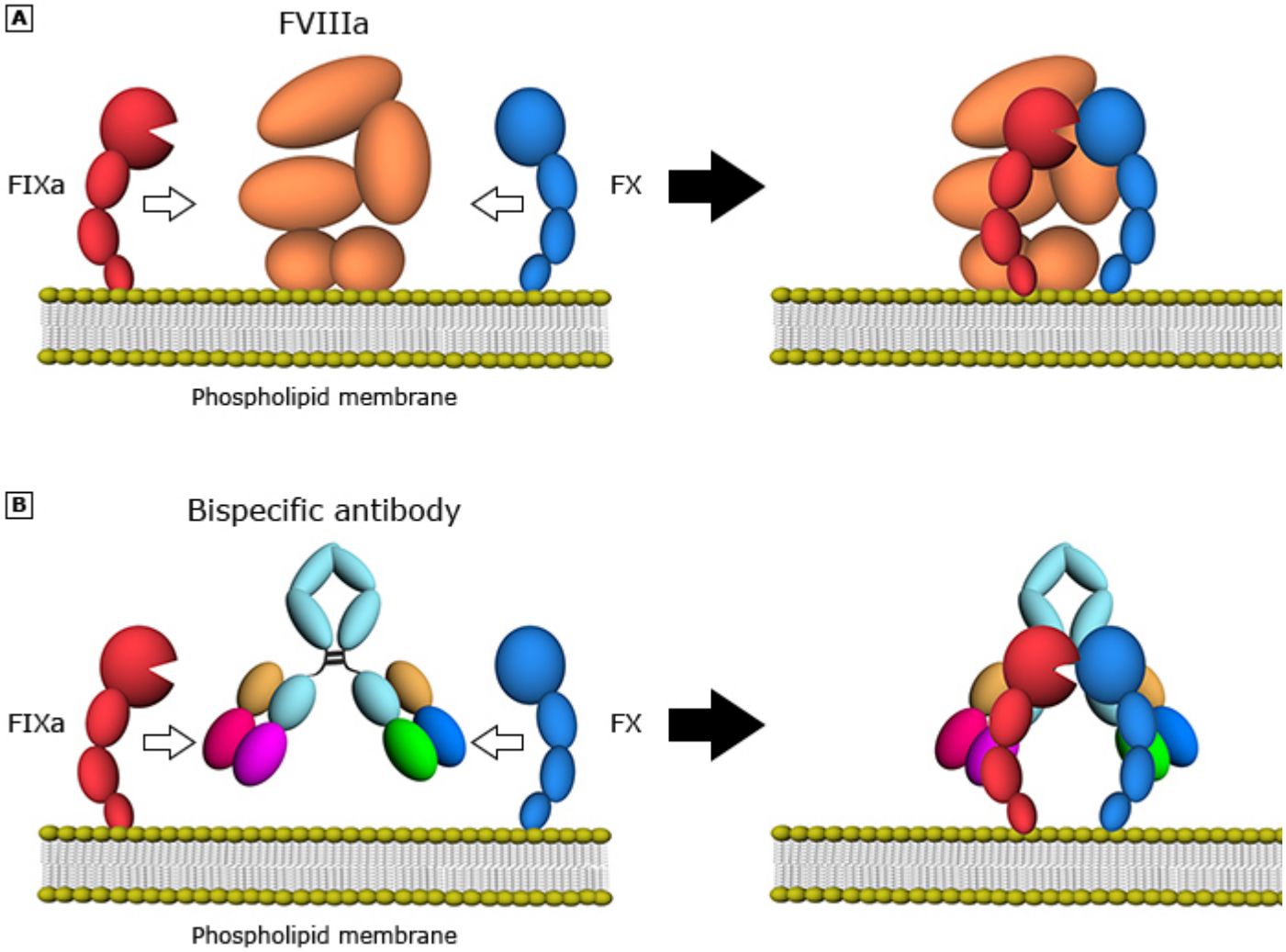
rFVIII: recombinant factor VIII; Fc: fragment crystallizable; VWF: von Willebrand factor; XTEN: half-life extension peptide.

Graphic 129483 Version 1.0

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).

Graphic 107801 Version 2.0