accredo®

Bleeding disorders

ER guide to bleeding disorders

Name:_____

Address:_____

Phone:_____

In case of emergency, contact: _____

Relation to patient:_____

Diagnosis:

❑ Hemophilia A: ❑ Mild ❑ Moderate ❑ Severe
❑ Inhibitors ❑ Inhibitors Bethesda units (if known) _____

❑ Hemophilia B: ❑ Mild ❑ Moderate ❑ Severe
❑ Inhibitors ❑ Inhibitors Bethesda units (if known) _____

❑ von Willebrand disease: ❑ Type 1 ❑ Type 2 ❑ Type 3 ❑ Platelet type

Preferred product:_____

Dose for life-threatening bleed:_____

If inhibitor, bypassing agent product name and dose:_____

Allergies:_____

Primary care physician:_____ Phone:_____

Hematologist or HTC:_____ Phone:_____

Table of contents

This *ER guide to bleeding disorders* contains general educational materials to assist emergency room staff in handling an emergency involving a patient with hemophilia or von Willebrand disease. This document is not intended to constitute medical advice or the rendering of medical care. The recommendations were developed by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF). The patient's hematologist should always be consulted with regard to the patient's medical treatment. The diagnosis and treatment of bleeding disorders should only be undertaken by, or under the direction of, a qualified doctor. Any questions should be directed to a qualified hematologist.

ER GUIDE TO BLEEDING DISORDERS

Inherited bleeding disorders, such as hemophilia and von Willebrand disease, present unique challenges for patients and caregivers in the emergency room (ER). Because hemophilia is rare — approximately 20,000 people in the United States have this bleeding disorder — many doctors may not have treated a patient with a bleeding disorder.[1,2]

This educational guide provides general recommendations and guidelines to assist emergency room staff in handling an emergency involving a patient with hemophilia or von Willebrand disease and is not intended to replace standard medical practices.

Diagnosis and treatment of bleeding disorders are the ultimate responsibility of the attending doctor. However, in many cases, the patients and caregivers are very knowledgeable about treatment. Any questions should be directed to a qualified hematologist.

In general, follow these guidelines:

- Do not keep this patient waiting.
- A bleeding episode requires immediate attention.
- Infuse promptly.
- Therapeutic infusions should precede radiographic studies, invasive procedures or complex evaluations.
- Listen to the patient.
- These patients are generally quite knowledgeable about the disease. Be prepared to work in collaboration with them.
- Contact the patient's hematologist.

GUIDELINES FOR EMERGENCY DEPARTMENT MANAGEMENT OF INDIVIDUALS WITH HEMOPHILIA

MASAC recommendation #175

The following guidelines were approved by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation on October 14, 2006, and adopted by the NHF Board of Directors on October 15, 2006.

Individuals with bleeding disorders who present to an emergency department for care should receive appropriate, expeditious management. To this end, MASAC has developed the following guidelines.

Triage

Triage should be urgent because delays in administering factor concentrate treatment significantly affect morbidity and mortality in individuals with hemophilia.

Assessment

1. Treatment for a suspected bleeding episode is based on clinical history. Physical exam findings tend to be normal in the early phases of most hemophilic bleeds. Spontaneous bleeding is common in individuals with severe disease (factor levels <1%). When in doubt, administer clotting factor replacement therapy.
2. Treatment decisions should be based on the suspicion of a bleeding-related problem, not the documentation of one.
3. Believe the patient or the parent of a patient. If in their experience they suspect occult bleeding is occurring, administer clotting factor replacement. Patients often are instructed in and/or carry with them appropriate factor replacement dosing guidelines as advised by their treating hematologist.
4. Consultation with the patient's hematologist or a regional hemophilia treatment center professional is strongly advised; however, this should not delay giving clotting factor replacement to the patient.

Diagnostic studies

1. Clotting factor replacement therapy should be given before any diagnostic studies (X-rays, CAT scans, etc.) are performed in the evaluation of a suspected bleeding problem, especially in the case of head trauma or suspected intracranial hemorrhage. For routine joint bleeding, no radiographic studies are indicated.
2. For patients with hemophilia who have illnesses or disorders that necessitate an invasive procedure (lumbar puncture, arterial blood gas, arthrocentesis, etc.) or surgery, factor replacement therapy must be administered in the emergency department beforehand.
3. For an individual with known hemophilia, routine laboratory studies (PT, PTT, factor levels) are not indicated in the treatment of a routine bleeding episode unless requested by the patient's hematologist. The clinical severity of a patient's hemophilia is gauged by his or her baseline clotting factor level, a value that remains fairly constant throughout that person's life.

Indications for factor replacement therapy

1. Suspected bleeding into a joint or muscle.
2. Any significant injury to the head, neck, mouth or eyes, or evidence of bleeding in those areas.
3. Any new or unusual headache, particularly one following trauma.
4. Severe pain or swelling at any site.
5. All open wounds requiring surgical closure, wound adhesive or steri-strips.
6. History of an accident or trauma that might result in internal bleeding.
7. Any invasive procedure or surgery.
8. Heavy or persistent bleeding from any site.
9. Gastrointestinal bleeding.
10. Acute fractures, dislocations and sprains.

TREATMENT

Hemophilia A without inhibitor

The treatment of choice for patients with hemophilia A (factor VIII deficiency) is recombinant factor VIII or the patient's product of choice. Plasma-derived concentrate is a suitable alternative in an emergency situation when recombinant factor VIII is not available. Cryoprecipitate and fresh frozen plasma are no longer recommended for treatment of people with hemophilia.

When bleeding is severe, the appropriate dose of factor VIII is **50 units/kg**. This should result in a factor VIII level of 80%–100%.

Mild hemophilia A with non-life- or limb-threatening bleeding

Individuals with mild hemophilia A (factor VIII greater than 5%) who are experiencing non-life- or limb-threatening bleeding may respond to desmopressin if they have been shown to respond to this treatment previously. Otherwise, treatment is the same as for other individuals with hemophilia A.

Hemophilia B without inhibitor

The treatment of choice for patients with hemophilia B (factor IX deficiency) is recombinant factor IX or the patient's product of choice. Plasma-derived concentrate is a suitable alternative in an emergency situation when recombinant factor IX is not available. Fresh frozen plasma is no longer recommended for treatment of individuals with hemophilia B. Note that cryoprecipitate does not contain factor IX. When bleeding is severe, the appropriate dose of factor IX is **100–120 units/kg.** This should result in a factor IX level of 80%–100%.

1. If a patient with hemophilia or the parent of a patient with hemophilia brings clotting factor with them to the emergency department, allow them to utilize it. They should be permitted to reconstitute the product and administer it whenever possible. Individuals with bleeding disorders are encouraged to have an emergency dose of factor concentrate or DDAVP in their home and to take it with them when they travel. In those situations where a patient does

not bring their own clotting factor concentrate, emergency departments must be prepared to provide clotting factor replacement. Emergency departments must have ready access to factor replacement products so they are available within 1 hour of the patient's arrival. In an effort to expedite care, emergency doctors should order unreconstituted factor from their pharmacy or blood bank and reconstitute the product in the emergency department.

2. Factor replacement must be administered intravenously by IV push over 1–2 minutes (or per manufacturer's recommendation).
3. Dose factor up to the "closest vial," and infuse the full content of each reconstituted vial. A moderate excess of factor concentrate will not create a hypercoaguable state but will prolong the therapeutic level of the product administered. Thus, it is prudent to "round up."
4. For individuals with inhibitors (antibodies to factor VIII), treatment decisions may be more complicated. The care of inhibitor patients should be urgently discussed with the patient's hematologist. If an individual with an inhibitor presents in a life- or limb-threatening scenario, the safest immediate action is to prescribe recombinant factor VIIa (rFVIIa) at a dose of **90 mcg/kg** or activated prothrombin complex concentrates FEIBA® VH at **75–100 units/kg**. The patient or family can also provide information on response to therapeutic bypassing agents.
5. When treating an individual with mild hemophilia A who is responsive to desmopressin, the dose and prior responsiveness are usually known. The dose of desmopressin is **0.3 mcg/kg** subcutaneously, or intravenously in **30 mL** normal saline over 30 minutes. It may also be administered as an ultra concentrated nasal spray (Stimate®) at a dose of one spray in one nostril for individuals <50 kg and one spray in each nostril for individuals >50 kg.
6. The most experienced IV therapist or phlebotomist should perform any venipuncture. Traumatic venipunctures and repeated needle sticks cause painful hematomas that may limit further IV access.
7. In any suspected bleeding emergency in which the clotting factor level of an individual with hemophilia is unknown, the factor level should be assumed to be 0 percent.
8. Intramuscular injections should be avoided if at all possible. If they must be given, factor replacement therapy should precede the injection. Parenteral agents should be given intravenously or subcutaneously. Tetanus immunizations may be administered subcutaneously.
9. In situations in which patients are hemodynamically stable and are not requiring volume replacement, the smallest gauge needle should be utilized for obtaining IV access (25-gauge butterfly needles in young infants, 23-gauge butterfly needles in older children and adults).
10. Tourniquets should not be applied tightly to extremities because they may cause bleeding.
11. Aspirin and aspirin-containing products are contraindicated in individuals with hemophilia A. Acetaminophen and/or codeine may be used for analgesia. Non-steroidal anti-inflammatory drugs (NSAIDs) may be carefully administered to select patients, such as individuals with chronic arthritic pain who are not actively bleeding or being treated for a recent bleeding problem.
12. If an individual with hemophilia A is bleeding and requires transportation to another facility for definitive care, all efforts should be made to replace the deficient clotting factor before transport.

This material is provided for your general information only. NHF does not give medical advice or engage in the practice of medicine. NHF under no circumstance recommends particular treatment for specific individuals and in all cases recommends that you consult your doctor or local treatment center before pursuing any course of treatment.

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TREATMENT OPTIONS AND GENERAL GUIDELINES

Clotting factor replacement therapy

An intravenous infusion of replacement clotting factor concentrate will elevate factor levels enough to allow the body to form a clot and stop the bleeding. Clotting factor concentrate comes as a freeze-dried powder that is reconstituted with sterile water prior to infusion. Factor must be used within 3 hours of reconstitution. Each box of factor has a lot number, expiration date and a specific number of units (assays). All this information should be included in the patient's chart when administered. Refer to the product manufacturer's package insert for specific mixing and dosing guidelines, administration rate and dosing calculations.

Reconstituted factor is injected into the body through a vein or a central venous access device. The smallest gauge needle should be utilized for obtaining IV access—25-gauge butterfly needles work well in young infants. Additionally, most adults and older children prefer butterfly needles for IV access—23-gauge needles are frequently used.

Dosage

Factor dosage or number of units infused is based on the patient's weight and the percentage of circulating factor VIII desired. Factor concentrates are manufactured in vials with varying assay ranges. Often, a factor prescription is written as +/- 10 percent of a target dose. To prevent costly waste of factor, full vials, rather than a portion of a vial, are administered for prescribed factor doses. A moderate excess of recombinant factor will prolong a therapeutic hemostatic level of the treatment. Try to match the assays with the calculated dosage as closely as possible. Overfilling increases drug utilization costs while underfilling may cause breakthrough or continuing bleeds, requiring follow-up infusions. Please refer to the dosage charts on pages 12 and 17 as a calculation guide.

Possible side effects

If infused too rapidly, side effects include tingling at the site or in the hands or lips, lightheadedness, shortness of breath and burning at the infusion site. Allergic reactions include chills, fever, hives and difficulty breathing.

Clotting factor concentrate

There are two forms of clotting factor concentrates, depending on the source from which it is made: plasma-derived or recombinant. Recombinant clotting factors are preferable and considered the standard treatment. Because recombinant products contain few or no proteins from human blood, the risk of contracting viruses is minimal or absent.

Cryoprecipitate, once regarded as the treatment of choice for people with hemophilia, is no longer recommended because it is considered less safe than currently available clotting factor concentrates.

Please refer to pages 14 and 15 for a list of factor VIII products and page 18 for a list of factor IX products available in the United States.

Treatment regimens

A patient's hematologist will prescribe a treatment regimen to manage hemophilia:

- **Episodic treatment** (also called on-demand or PRN) occurs when factor is given only when a bleeding episode occurs.
- **Prophylaxis** is the practice of giving factor on a regular basis (usually several times a week) to raise factor levels to prevent bleeds.
- **Planned preventive treatment** involves infusing factor before an event or activity that may potentially cause a bleed.
- **Continuous infusion** is when factor is delivered through a continuous ambulatory infusion pump. This delivery mode is often used to stop bleeding for hemophilia patients who face surgery, trauma or serious hemorrhage. Studies have shown that continuous infusion maintains factor level in a therapeutic range and provides effective hemostasis compared with bolus injection. However, continuous infusion of factor requires different dosing calculations. Please consult a hematologist for more information. **Note:** Continuous infusion is currently used off-label and is not approved by the FDA.

MEDICATIONS

Desmopressin, Stimate, Amicar®

Patients with mild hemophilia A (baseline clotting factor of at least 5 percent) who have non-life–threatening bleeding may be given desmopressin either intravenously, subcutaneously, or intranasally. Because desmopressin is a potent antidiuretic agent, the patient must restrict fluid intake, and serum sodium levels should be monitored during repeated doses of the drug.[1]

Amicar (aminocaproic acid) is often used to treat mouth bleeds. It is available in injectable, tablet and liquid forms. This product should not be used in conjunction with anti-inhibitor or factor IX products or bypassing agents, such as FEIBA VH.

Prescriptions, over-the-counter medications and herbal supplements

It is important to know what medications the patient is taking, including herbs, vitamins and over-the-counter drugs. Certain drugs may interact with each other or make it harder for blood to clot. A complete medication profile will allow you to check for any possible interactions.

Acetaminophen

Because aspirin can be harmful to people with bleeding disorders, many hematologists recommend acetaminophen for their patients.

Anticoagulants and anti-platelet agents

Anticoagulants, or blood thinners, by their very nature may lead to bleeding complications if not closely monitored. If these medications are needed, monitoring by a doctor is essential.

Bile acid sequestrants

These drugs lower cholesterol by binding to bile acids and decreasing the amount of fat and lipid material absorbed by the body. While these drugs do not cause bleeding complications directly, continued use may lead to a decrease in the absorption of vitamin K, which is needed for effective clotting.

COX-2 inhibitors

A COX-2 inhibitor, such as celecoxib, is a type of NSAID that causes fewer bleeding problems than traditional NSAIDs. COX-2 inhibitors are often used to treat arthritis and are not associated with causing platelets to malfunction. The National Hemophilia Foundation recommends the potential risk of bleeding be weighed against the potential benefit in patients with bleeding disorders.[4,5]

Non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates

These medications are used for pain and inflammation. They have the potential to prolong bleeding by preventing platelets from sticking to one another. These medications can also irritate the stomach and cause bleeding. Aspirin should not be taken by a person with a bleeding disorder. Aspirin can also prevent platelets from working properly and worsen a patient's underlying tendency to bleed.

Interferon and ribavirin

Interferons are used to treat viral infections and various types of cancer. Gastrointestinal bleeding has been associated with alpha interferon. Anemia has been associated with the use of both interferon and ribavirin, which is also used to treat hepatitis.[6]

Protease inhibitors

Protease inhibitors are used in combination with other antiretroviral medications in the treatment of HIV infection. These medications can be used in patients with bleeding disorders under the supervision of a doctor. Some patients taking these medications have reported spontaneous bleeding.

Natural products

A number of herbal products may affect bleeding time, the formation of a clot or the ability of platelets to stick together to form a clot.

Pain management

When treating the pain that typically accompanies a hemorrhage, avoid giving drugs that inhibit platelet aggregation. Never give aspirin, agents that contain aspirin or other NSAIDs that inhibit platelet aggregation. Acetaminophen and opiate agents are preferable.

The following is a list of specific drugs that affect clotting. This is not a complete list.

Anti-coagulants
Dalteparin (Fragmin®)
Enoxaparin (Lovenox®)
Fondaparinux (Arixtra®)
Heparin
Tinzaparin (Innohep®)
Warfarin (Coumadin®)

Anti-platelet agents
Cilostazol (Pletal®)
Clopidogrel (Plavix®)
Ticlopidine (Ticlid®)
Anagrelide (Agrylin®)
Dipyridamole (Persantine,® Aggrenox®)

Bile acid sequestrants
Cholestyramine (Questran,® Lo Cholest®)
Colestipol (Colestid®)
Colesevelam (Welchol™)

Herbal Products
Anise
Astragalus
Bilberry
Bromelain
Dong quai
Fish oils (omega 3 fatty acids)
Flax seed
Fucus
Garlic
Ginger
Ginko biloba
Ginseng
Guarana
Horse chestnut

Pennyroyal
St. John's wort
Tumeric
Vitamin E

NSAIDs
Celecoxib (Celebrex®)
Diclofenac (Cataflam,® Voltaren,® Arthrotec®—combination with misoprostol)
Diflunisal (Dolobid®)
Etodolac (Lodine,® Lodine® XL)
Flurbiporfen (Ansaid®)
Ibuprofen (Motrin,® Advil,® Nuprin®)
Indomethacin (Indocin,® Indocin® SR)
Ketoprofen (Orudis,® Orudis® KT, Oruvail®)
Ketorolac (Toradol®)
Meloxicam (Mobic®)
Nabumetone (Relafen®)
Naproxen (Aleve,® Anaprox,® Naprosyn®)
Oxaprozin (Daypro®)
Piroxicam (Feldene®)
Sulindac (Clinoril®)
Tolmentin (Tolectin®)

Protease inhibitors
Amprenavir (Agenerase®)
Atazanavir sulfate (Reyataz®)
Darunavir (Prezista®)
Fosamprenavir (Lexiva®)
Indinivir sulfate (Crixivan®)
Lopinavir/ritonavir (Kaletra®)
Nelfinavir mesylate (Viracept®)
Ritonavir (Norvir®)
Saquinavir mesylate (Invirase,® Fortovase®)
Tipranavir (Aptivus®)

Salicylates
Aspirin (Bufferin,® Excedrin, Anacin,® and many others)
Magnesium salicylate (Extra Strength Doan's®)
Salicylate combinations (Trilisate®)

HEMOPHILIA A

Hemophilia A is rare, affecting only 12,000 people in the United States.[7]

What is hemophilia A?

People who are missing or have a low amount of factor VIII have hemophilia A. There are different levels of severity of hemophilia, determined by the amount of factor a person has in his blood. Severity levels do not change over time.

MASAC recommendations concerning the treatment of hemophilia A

MASAC recommendation #187

(Replaces document #182)

(Revised November 2008)

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on November 15, 2008, and adopted by the NHF Board of Directors on November 16, 2008.

I. Recommendation for doctors treating patients with hemophilia A

A. Treatment of hemophilia A

1. Recombinant factor VIII concentrates: Recombinant (r) FVIII is produced by well-established hamster cell lines that have been transfected with the gene for human FVIII(1,2). Two recombinant factor VIII products have the B domain deleted from the factor VIII gene before it is inserted into Chinese hamster ovary cells (3). First generation rFVIII contains animal and/or human plasma-derived proteins in the cell culture medium and in the final formulation vial. Second generation rFVIII contains animal or human plasma proteins in the medium but not in the final formulation, while third generation rFVIII does not contain any animal or human plasma-derived proteins in the culture medium or in the final formulation vial. The risk of human viral contamination associated with recombinant FVIII is definitely much lower than for plasma-derived FVIII products. No seroconversions to HIV, HBV or HCV have been reported with any of the currently available products; thus, recombinant factor VIII products are the recommended treatment of choice for patients with hemophilia A. (Table I.A.)
2. Plasma-derived factor VIII concentrates: Improved viral-depleting processes and donor screening practices have resulted in plasma-derived (pd) FVIII products that have greatly reduced risk for transmission of human immunodeficiency virus and hepatitis B and C. No seroconversions to HIV, HBV or HCV have been reported with any of the pdFVIII products currently marketed in the United States, including products that are heated in aqueous solution (pasteurized), solvent-detergent treated and/or immunoaffinity purified. Thus, each of these methods appears to have greatly reduced the risk of viral transmission compared with older methods of viral inactivation (4–6). There remains the possibility of HIV-1, HIV-2 or hepatitis B or C virus transmission with the use of currently marketed, viral-inactivated, plasma-derived products. The non-lipid enveloped viruses human parvovirus B19 and hepatitis A virus were also transmitted by pdFVIII (7–9); additional steps such as viral filtration have been added to reduce these risks as well. (Table I.B.).
3. Cryoprecipitate not recommended: FVIII products are available that are manufactured by recombinant technology and thus theoretically do not transmit human viruses. Moreover, methods of viral inactivation (pasteurization, solvent-detergent treatment, immunoaffinity purification) have resulted in a reduced risk of HIV and hepatitis B and C transmission with plasma-derived factor VIII concentrates (5–6, 11–13). For these reasons, cryoprecipitate should not be used as a treatment alternative. Despite donor screening by nucleic acid testing (NAT) for HIV-1, HBV and HCV, cryoprecipitate might still be infectious. While the current estimate for the risk of HIV infection from a single unit of blood is one in 1,000,000 donations, the risk of HCV transmission is somewhat higher, approximately 1 in 900,000 (14).
4. Treatment of mild hemophilia A: Desmopressin (DDAVP®) should be used whenever possible for patients with mild hemophilia A. DDAVP is available in both a parenteral form (DDAVP injection) and a highly concentrated intranasal spray formulation (Stimate nasal spray). (Table III.A.) Desmopressin should not be used in certain categories of patients. Children under the age of 2, pregnant women and patients with mild hemophilia A in whom desmopressin does not provide adequate factor VIII levels should be treated as per section I.A.1 or I.A.2.

Classification	Factor level	What to expect[8]
Severe	Less than 1%	Bleeding after a minor injury, major trauma or surgery is common. Bleeding may occur without an obvious injury (spontaneous bleeding).
Moderate	1 to 5%	Bleeding after minor injury is possible, as well as after major trauma or surgery. Occasional spontaneous bleeding may occur but is usually associated with prolonged or serious bleeding in a joint.
Mild	5 to 30%	5 to 30 percent. Prolonged bleeding usually occurs only after serious injury, major trauma or surgery.
Normal	50 to 150%	50 to 150 percent. No abnormal bleeding.

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Dosage chart for factor VIII (hemophilia A only)

Weight		Percentage of circulating factor VIII desired											
lbs	kgs	10%	15%	20%	25%	30%	40%	50%	60%	70%	80%	90%	100%
20	9.1	45	68	91	114	136	182	227	273	318	364	409	455
30	13.6	68	102	136	170	205	273	341	409	477	545	614	682
40	18.2	91	136	182	227	273	364	455	545	636	727	818	909
50	22.7	114	170	227	284	341	455	568	682	795	909	1023	1136
60	27.3	136	205	273	341	409	545	682	818	955	1091	1227	1364
70	31.8	159	239	318	398	477	636	795	955	1114	1273	1432	1591
80	36.4	182	273	364	455	545	727	909	1091	1273	1455	1636	1818
90	40.9	205	307	409	511	614	818	1023	1227	1432	1636	1841	2045
100	45.5	227	341	455	568	682	909	1136	1364	1591	1818	2045	2273
110	50	250	375	500	625	750	1000	1250	1500	1750	2000	2250	2500
120	54.5	273	409	545	682	818	1091	1364	1636	1909	2182	2455	2727
130	59.1	295	443	591	739	886	1182	1477	1773	2068	2364	2659	2955
140	63.6	318	477	636	795	955	1273	1591	1909	2227	2545	2864	3182
150	68.2	341	511	682	852	1023	1364	1705	2045	2386	2727	3068	3409
160	72.7	364	545	727	909	1091	1455	1818	2182	2545	2909	3273	3636
170	77.3	386	580	773	966	1159	1545	1932	2318	2705	3091	3477	3864
180	81.8	409	614	818	1023	1227	1636	2045	2455	2864	3273	3682	4091
190	86.4	432	648	864	1080	1295	1727	2159	2591	3023	3455	3886	4318
200	90.9	455	682	909	1136	1364	1818	2273	2727	3182	3636	4091	4545
210	95.5	477	716	955	1193	1432	1909	2386	2864	3341	3818	4295	4773
220	100	500	750	1000	1250	1500	2000	2500	3000	3500	4000	4500	5000
230	104.5	523	784	1045	1307	1568	2091	2614	3136	3659	4182	4705	5227
240	109.1	545	818	1091	1364	1636	2182	2727	3273	3818	4364	4909	5455
250	113.6	568	852	1136	1420	1705	2273	2841	3409	3977	4545	5114	5682

The above dosage chart is for people who have hemophilia A (factor VIII deficiency).

To determine the appropriate percentage of circulating clotting factor needed, contact a hemophilia treatment center or hematologist.

Dosages are given in assays (number of units) to correspond with units per bottle.

Available assays (units per bottle) may not be exact to dosage chart. If the amount mixed has a variance of +/- 10%, please contact a hematologist.

Entire contents of reconstituted factor bottle should be used within 3 hours of mixing.

Example using dosage chart:

A man weighing 160 lbs. needs to raise his factor level to 40%. Using this chart, he would require 1455 units of factor VIII concentrate. If the factor VIII concentrate bottles on hand contain 730 units each, the man will receive two bottles.

TABLE I. Products licensed in the U.S. to treat hemophilia A (MASAC recommendation #187)

A. Recombinant factor VIII products

Product name	Manufacturer	Method of viral depletion or inactivation	Stabilizer in final vial	Heparin in final vial	Human or animal plasma-derived protein used in culture medium	Generation	Specific activity of final product (IU factor VIII/mg total protein after addition of stabilizer)	Viral safety studies in humans with this product
Advate™	Baxter	1. Immunoaffinity chromatography 2. Solvent/detergent (TNBP/Polysorbate 80)	Trehalose	None	None	Third	4,000–10,000	Yes
Helixate® FS	Bayer (distributed by CSL Behring)	1. Immunoaffinity chromatography 2. Solvent/detergent (TNBP/Polysorbate 80)	Sucrose, 28 mg/vial	None	Human plasma protein solution	Second	4,000	Yes
Kogenate® FS	Baxter	1. Immunoaffinity chromatography 2. Solvent/detergent (TNBP/Polysorbate 80)	Sucrose, 28 mg/vial	None	Human plasma protein solution	Second	4,000	Yes
Recombinate™	Bayer	1. Immunoaffinity chromatography	Human albumin	None	Bovine serum albumin	First	1.65–19	Yes
ReFacto®	Wyeth	1. Immunoaffinity chromatography 2. Solvent/detergent (TNBP/Triton X-100)	Sucrose	None	Human serum albumin (manufactured by Instituto Grifols, Spain, OctaPharma, Sweden)	Second (B-domain deleted)	9,110–13,700	Yes
Xyntha™	Wyeth	1. Solvent/detergent (TNBP/Polysorbate 80) 2. Nanofiltration	Sucrose	None	None	Third (B-domain deleted)	5,500–9,900	Yes

TABLE I. Products licensed in the U.S. to treat hemophilia A (MASAC recommendation #187)

B. Immunoaffinity purified factor VIII products derived from human plasma

Product name	Manufacturer	Method of viral inactivation	Heparin in final vial	Specific activity of final product (IU factor VIII/mg total protein after addition of stabilizer)	Viral safety studies in humans with this product	Viral safety studies in humans with another product, but similar viral inactivation method
Hemofil® M	Baxter	1. Immunoaffinity chromatography 2. Solvent/detergent (TNBP/Octoxynol 9)	None	2–20	Yes	No
Monarc-M®	Baxter (from American Red Cross—collected plasma)	1. Immunoaffinity chromatography 2. Solvent/detergent (TNBP/Octoxynol 9)	None	2–20	No	Yes
Monoclate® P	CSL Behring	1. Immunoaffinity chromatography 2. Pasteurization (60°C, 10h)	None	5–10	Yes	Yes

HEMOPHILIA B

Hemophilia B is rare, affecting only 5,000 people in the United States.[9]

What is hemophilia B?

People who are missing or have a low amount of factor IX have hemophilia B. There are different levels of severity of hemophilia B determined by the amount of factor a person has in his/her blood. Severity levels do not change over time.

MASAC recommendations concerning the treatment of hemophilia B

MASAC recommendation #187

(Replaces document #182)

(Revised November 2008)

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on November 15, 2008, and adopted by the NHF Board of Directors on November 16, 2008.

I. Recommendation for doctors treating patients with hemophilia B

B. Treatment of hemophilia B

1. Recombinant factor IX concentrate: Recombinant factor IX (rFIX) is produced in Chinese hamster ovary cells; no human or animal plasma-derived proteins are used in the manufacturing process. It is stabilized with sucrose (third generation product). Thus, the risk of human blood-borne viral contamination is essentially zero (15). Recombinant factor IX is considered to be the treatment of choice for patients with hemophilia B. (Table II. A.)
2. Plasma-derived factor IX concentrates: Improved viral depleting processes and donor screening practices have resulted in plasma-derived (pd) FIX products with greatly reduced risk for HIV, HBV and HCV transmission (16). Viral attenuation methods used in the production of pdFIX products that appear to be effective for reducing the risk of HIV and hepatitis are dry heating at 60°C for 144 hours, solvent-detergent treatment, vapor treatment and sodium thiocyanate plus ultrafiltration. Purification steps involved in the preparation of the more purified pd-coagulation FIX products are associated with loss of several additional logs of virus. A slight possibility of viral transmission with the currently marketed viral inactivated, plasma-derived products remains. Transmission of human parvovirus B19 and hepatitis A virus by these products did occur, but the risk has been reduced with additional viral attenuation methods such as ultrafiltration. (Table II. B.)
3. Reduction of thromboembolic risk during surgery: The use of recombinant factor IX or pd coagulation FIX concentrates rather than pd-prothrombin complex concentrates (PCCs) is recommended in certain situations associated with a higher risk of thromboembolic complications, such as surgery or severe hemorrhage requiring treatment one to two times per day. (Table II. A. Table II. B.)

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Classification	Factor level	What to expect[8]
Severe	Less than 1%	Bleeding after a minor injury, major trauma or surgery is common. Bleeding may occur without an obvious injury (spontaneous bleeding).
Moderate	1 to 5%	Bleeding after minor injury is possible, as well as after major trauma or surgery. Occasional spontaneous bleeding may occur but is usually associated with prolonged or serious bleeding in a joint.
Mild	5 to 30%	5 to 30 percent. Prolonged bleeding usually occurs only after serious injury, major trauma or surgery.
Normal	50 to 150%	50 to 150 percent. No abnormal bleeding.

Dosage chart for factor IX (hemophilia B only)

Weight		Percentage of circulating factor IX desired											
lbs	kgs	10%	15%	20%	25%	30%	40%	50%	60%	70%	80%	90%	100%
20	9.1	91	136	182	227	273	364	455	545	636	727	818	909
30	13.6	136	205	273	341	409	545	682	818	955	1091	1227	1364
40	18.2	182	273	364	455	545	727	909	1091	1273	1455	1636	1818
50	22.7	227	341	455	568	682	909	1136	1364	1591	1818	2045	2273
60	27.3	273	409	545	682	818	1091	1364	1636	1909	2182	2455	2727
70	31.8	318	477	636	795	955	1273	1591	1909	2227	2545	2864	3182
80	36.4	364	545	727	909	1091	1455	1818	2182	2545	2909	3273	3636
90	40.9	409	614	818	1023	1227	1636	2045	2455	2864	3273	3682	4091
100	45.5	455	682	909	1136	1364	1818	2273	2727	3182	3636	4091	4545
110	50	500	750	1000	1250	1500	2000	2500	3000	3500	4000	4500	5000
120	54.5	545	818	1091	1364	1636	2182	2727	3273	3818	4364	4909	5455
130	59.1	591	886	1182	1477	1773	2364	2955	3545	4136	4727	5318	5909
140	63.6	636	955	1273	1591	1909	2545	3182	3818	4455	5091	5727	6364
150	68.2	682	1023	1364	1705	2045	2727	3409	4091	4773	5455	6136	6818
160	72.7	727	1091	1455	1818	2182	2909	3636	4364	5091	5818	6545	7273
170	77.3	773	1159	1545	1932	2318	3091	3864	4636	5409	6182	6955	7727
180	81.8	818	1227	1636	2045	2455	3273	4091	4909	5727	6545	7364	8182
190	86.4	864	1295	1727	2159	2591	3455	4318	5182	6045	6909	7773	8636
200	90.9	909	1364	1818	2273	2727	3636	4545	5455	6364	7273	8182	9091
210	95.5	955	1432	1909	2386	2864	3818	4773	5727	6682	7636	8591	9545
220	100	1000	1500	2000	2500	3000	4000	5000	6000	7000	8000	9000	10000
230	104.5	1045	1568	2091	2614	3136	4182	5227	6273	7318	8364	9409	10455
240	109.1	1091	1636	2182	2727	3273	4364	5455	6545	7636	8727	9818	10909
250	113.6	1136	1705	2273	2841	3409	4545	5682	6818	7955	9091	10227	11364

The above dosage chart is for people who have hemophilia B (factor IX deficiency).

To determine the appropriate percentage of circulating clotting factor needed, contact a hemophilia treatment center or hematologist.

Dosages are given in assays (number of units) to correspond with units per bottle.

Available assays (units per bottle) may not be exact to dosage chart. If the amount of factor mixed has a variance of +/- 10%, please contact a hematologist.

Entire contents of reconstituted factor bottle should be used within 3 hours of mixing.

Example using dosage chart:

A man weighing 160 lbs. needs to raise his factor level to 40%. Using this chart, he would require 2909 units of factor IX concentrate. If the factor IX concentrate bottles on hand contain 1450 units each, the man will receive two bottles.

TABLE II. Products licensed in the U.S. to treat hemophilia B (MASAC recommendation #187)
A. Recombinant factor IX products

Product name	Manufacturer	Method of viral inactivation	Stabilizer in final vial	Heparin in final vial	Human or animal plasma-derived protein used in culture medium	Generation	Specific activity of final product (IU factor IX/mg total protein)	Viral safety studies in humans with this product
BeneFIX®	Wyeth	1. Affinity chromatography 2. Viral filtration	Sucrose	None	None	Third	200–360	Yes

TABLE II. Products licensed in the U.S. to treat hemophilia B (MASAC recommendation #187)
B. Coagulation factor IX products derived from human plasma

Product name	Manufacturer	Method of viral depletion or inactivation	Heparin in final vial (Units/IU factor IX)	Specific activity of final product (IU factor IX/mg total protein after addition of stabilizer)	Viral safety studies in humans with this product	Viral safety studies in humans with another product, but similar viral inactivation method
AlphaNine® SD	Grifols	1. Dual affinity chromatography 2. Solvent/detergent (TNBP/Polysorbate 80) 3. Nanofiltration (viral retention filter)	0.04	>150	Yes	Yes
Mononine®	CSL Behring	1. Immunoaffinity chromatography 2. Sodium thiocyanate 3. Ultrafiltration	None	>190	Yes	No

HEMOPHILIA A AND B WITH INHIBITORS[10]

For patients with inhibitors (antibodies to factor VIII and factor IX), treatment decisions are more complicated. The care of inhibitor patients should be urgently discussed with the patient's hematologist. Treating a person who has inhibitors can be a challenging experience for both the patient and the healthcare team. Often the treatment is a twofold process: managing bleeding episodes first, while dealing with the inhibitor itself secondly. Dealing with the presence of inhibitors can take months or even years of treatment.

What are inhibitors?

In some cases when a patient receives replacement factor, the body's immune system will perceive the normal clotting factor as foreign or as an antigen to which an antibody is produced. These antibodies are called inhibitors. The inhibitor binds to the infused clotting factor, making it difficult—if not impossible—to obtain a level sufficient to control bleeding. Treatment with replacement clotting factor does not have the same long-term, positive outcomes as in patients without inhibitors. These less-than-optimal treatments can also lead to secondary problems, such as infections, bleeding into joints and organ damage.

Because of these complications, many healthcare providers believe ridding the body of inhibitors is the best option, using a course of therapy known as "immune tolerance." There are different immune tolerance treatment programs, but most require repeated exposure to the deficient clotting factor. People who opt for immune tolerance infuse daily doses of factor over a period of weeks or, in some cases, years. Some people using this therapy also receive immunosuppressive drugs, which can predispose them to infections. The risks and benefits of each treatment program should be discussed in detail with a healthcare provider. The goal of immune tolerance therapy is to "teach" the body to tolerate the factor, rather than mount an immune response, so normal replacement therapy can be used to prevent or control bleeding. Overall, immune tolerance treatment is thought to work 60–80 percent of the time.

Low-responding inhibitors

For patients who have low-responding inhibitor levels (i.e., low levels of inhibitor in the blood), continued therapy with factor replacement is often possible. This therapeutic approach provides control of both minor and more serious bleeds. To overcome the presence of inhibitors in these cases, doctors may use larger doses of factor and may need to provide additional doses.

High-responding inhibitors

For people with high-responding inhibitors, utilizing standard factor is, in many cases, not possible because the inhibitor neutralizes even the largest possible dose of factor. Specialty products that bypass factor VIII and factor IX in the clotting cascade are generally needed. In these cases, treatment is based on the type of hemophilia and the nature of the bleed.

MASAC recommendations concerning the treatment of patients with inhibitors to factor VIII or IX

MASAC recommendation #187

(Replaces document #182)

(Revised November 2008)

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on November 15, 2008, and adopted by the NHF Board of Directors on November 16, 2008.

I. Recommendation for doctors treating patients with hemophilia with inhibitors.

D. Treatment of patients with inhibitors to factor VIII or IX:

The following products have been licensed for use in patients with inhibitors. However, the products are not interchangeable. Choice of product depends on multiple factors, including type of inhibitor (low- or high-responding), current titer of inhibitor, location of the bleed and availability of these products. Consultation with a hemophilia treatment center is strongly recommended.

1. Activated prothrombin complex concentrate (aPCC): aPCC contains activated factors IIa, VIIa, and Xa. These factors are able to bypass an inhibitor to factor VIII or factor IX to promote hemostasis. This product is derived from human plasma and is treated with vapor (steam) heat to eliminate viruses (22). (Table IV. A.)
2. Recombinant factor VIIa concentrate: Recombinant factor VIIa is licensed for use in patients with inhibitors to factor VIII or IX. It is produced by baby hamster kidney cells; animal—not human proteins—are used in its production. It is stabilized with mannitol (second-generation recombinant product). Thus, the risk of transmission of human viruses is essentially zero (23). (Table IV. B.)

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TABLE IV. Products licensed in the U.S. to treat inhibitor patients (MASAC recommendations #187)

A. Anti-inhibitor coagulation complex (activated prothrombin complex concentrates) derived from human plasma (for use in patients with inhibitors to factor VIII or IX)

Product name	Manufacturer	Method of viral depletion or inactivation	Heparin in final vial (units/mL)	Specific activity of final product (IU factor/mg total protein after addition of stabilizer)	Viral safety studies in humans with this product	Viral safety studies in humans with another product, but similar viral inactivation method
FEIBA VH	Baxter (Vienna)	Vapor heat (10h, 60°C, 190 mbar plus 1h, 80°C, 375 mbar)	None	0.8	Yes	Yes

TABLE IV. Products licensed in the U.S. to treat inhibitor patients (MASAC recommendations #187)

B. Recombinant factor VIIa for use in patients with inhibitors to factor VIII or IX

Product name	Manufacturer	Method of viral depletion or inactivation	Stabilizer in final vial	Heparin in final vial (units/mL)	Human or animal plasma-derived protein used in culture medium	Generation	Viral safety studies in humans with this product
NovoSeven®	Novo Nordisk (Bagsvaerd, Denmark)	1. Affinity chromatography 2. Solvent/detergent (TNPB/polysorbate 80)	Mannitol	None	Newborn calf serum	Second	Yes

NOTE: ***NovoSeven has been replaced by NovoSeven RT.***

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VON WILLEBRAND DISEASE

What is von Willebrand disease?[11, 12]

Von Willebrand disease (vWD) is a hereditary bleeding disorder characterized by bleeding from the skin and mucous membranes (e.g., mouth, nose, throat, gastrointestinal tract). The most common symptoms of von Willebrand disease are easy bruising, prolonged nosebleeds, heavy or prolonged menstrual periods (lasting more than 7 days) and prolonged bleeding following injury, surgery, dental procedures and childbirth. Gastrointestinal bleeding can also occur.

People with von Willebrand disease have a deficiency or defect in a blood-clotting protein called von Willebrand factor (vWF). Von Willebrand disease differs from hemophilia because it affects both males and females equally. It is the most common inherited bleeding disorder, affecting approximately one percent of the population.

What are the different types of von Willebrand disease?

There are several types of von Willebrand disease that are determined by diagnostic blood tests. Because the type and subtype determine treatment, it is important to know the specific type of von Willebrand disease.

Type 1 is the most common type of vWD, accounting for approximately 90 percent of all cases. People with this type have reduced levels of von Willebrand factor. Bleeding symptoms are usually mild.

Type 2 includes subtypes 2A, 2B, 2M and 2N. People with this type have a defect in the von Willebrand factor they produce, so it does not work properly. People with Type 2 von Willebrand disease usually have mild to moderate symptoms. Each subtype is treated differently, so knowing the exact subtype is important in determining the course of treatment.

Type 3 occurs when there is an absence or very low levels of von Willebrand factor and factor VIII. Type 3 vWD is considered severe. In this rare type of von Willebrand disease, patients can experience frequent bleeding—including in the joints and muscles—similar to people with hemophilia.

MASAC recommendations regarding the treatment of von Willebrand disease

MASAC recommendation #186

(Replaces document #173)

The following recommendations were approved by the Medical and Scientific Advisory Council (MASAC) on November 15, 2008, and adopted by the NHF Board of Directors on November 16, 2008.

Von Willebrand disease is the most common inherited bleeding disorder. Recent studies estimate the incidence at one to two percent of the general population. Since it is inherited in an autosomal dominant fashion, males and females are equally affected. Von Willebrand disease is associated with mucus membrane bleeding, excessive bruising and bleeding from cuts. It can result in excessive bleeding with invasive dental work, during surgical procedures and after accident or injury. In women, excessive menstrual bleeding is often the major symptom. Women with von Willebrand disease are also at risk of postpartum hemorrhage, particularly delayed postpartum hemorrhage.

Recently developed products have changed the treatment options for individuals with von Willebrand disease. The following are current recommendations for treating bleeding in these individuals.

1. Persons with Type 1 von Willebrand disease should be treated with the synthetic agent desmopressin (DDAVP injectable or Stimate nasal spray for bleeding, 1.5 mg/mL). Their response at first use should be documented for future reference. For surgery, trauma or other serious bleeding episodes, if hemostasis is not achieved with DDAVP, a factor VIII concentrate rich in the high molecular weight multimers of von Willebrand factor should be used (see #3 below).
2. Persons with type 2A, 2M and 2N von Willebrand disease should be treated with DDAVP if they have been shown by a DDAVP trial to be responsive.
3. Persons with type 2B and type 3 von Willebrand disease—and those with type 1, 2A, 2M and 2N who have been shown to be nonresponsive to DDAVP should be treated with a factor VIII concentrate that is known to contain the higher molecular weight multimers of von Willebrand factor and that has been virally attenuated to eliminate transmission of HIV and hepatitis A, B and C. Alphanate® (Grifols) and Humate-P® (CSL-Behring) have been approved by the FDA for use in vWD. Koate®-DVI (Talecris) may also be effective in these patients, but it has not been approved by the FDA for use in von Willebrand disease.
4. Because of the increased risk of HIV and hepatitis A, B and C transmission, cryoprecipitate should not be used except in an emergency situation where one of the above-mentioned products is not available and delay of treatment would be life- or limb-threatening.
5. Desmopressin is a potent antidiuretic agent, and fluid retention is a potential complication of this drug. Both parenterally administered DDAVP and Stimate nasal spray have been associated with the development of hyponatremia and seizures. To minimize this risk, the following precautions should be observed when this drug is used at home:
   a. DDAVP and Stimate should be administered no more often than once every 24 hours.
   b. DDAVP and Stimate should be used for no more than 3 consecutive days unless

directed to do so by hemophilia treatment center medical staff.

c. DDAVP and Stimate should not be used in children under the age of 2 years.

d. DDAVP and Stimate should be used with caution in the elderly and in individuals with a history of heart disease, hypertension or stroke.

e. If a patient is treated with DDAVP before surgery, the anesthesiologist should be advised to avoid fluid overload and dilutional hyponatremia.

f. DDAVP should be used with extreme caution in pregnant women and in women who are immediately postpartum.

6. An adjunctive treatment for mucous membrane bleeding is the antifibrinolytic agent aminocaproic acid (Amicar). This agent can be given orally or intravenously.

7. Prior to surgery in a patient with von Willebrand disease, consultation should be obtained with a pediatric or adult hematologist who specializes in the management of individuals with inherited bleeding disorders. This consultation should cover such issues as the need for a DDAVP stimulation test; type of fluid replacement/fluid restriction; dose and duration if DDAVP is to be used; appropriate dose, timing and duration of factor replacement therapy; and use of adjunctive medications (Amicar).

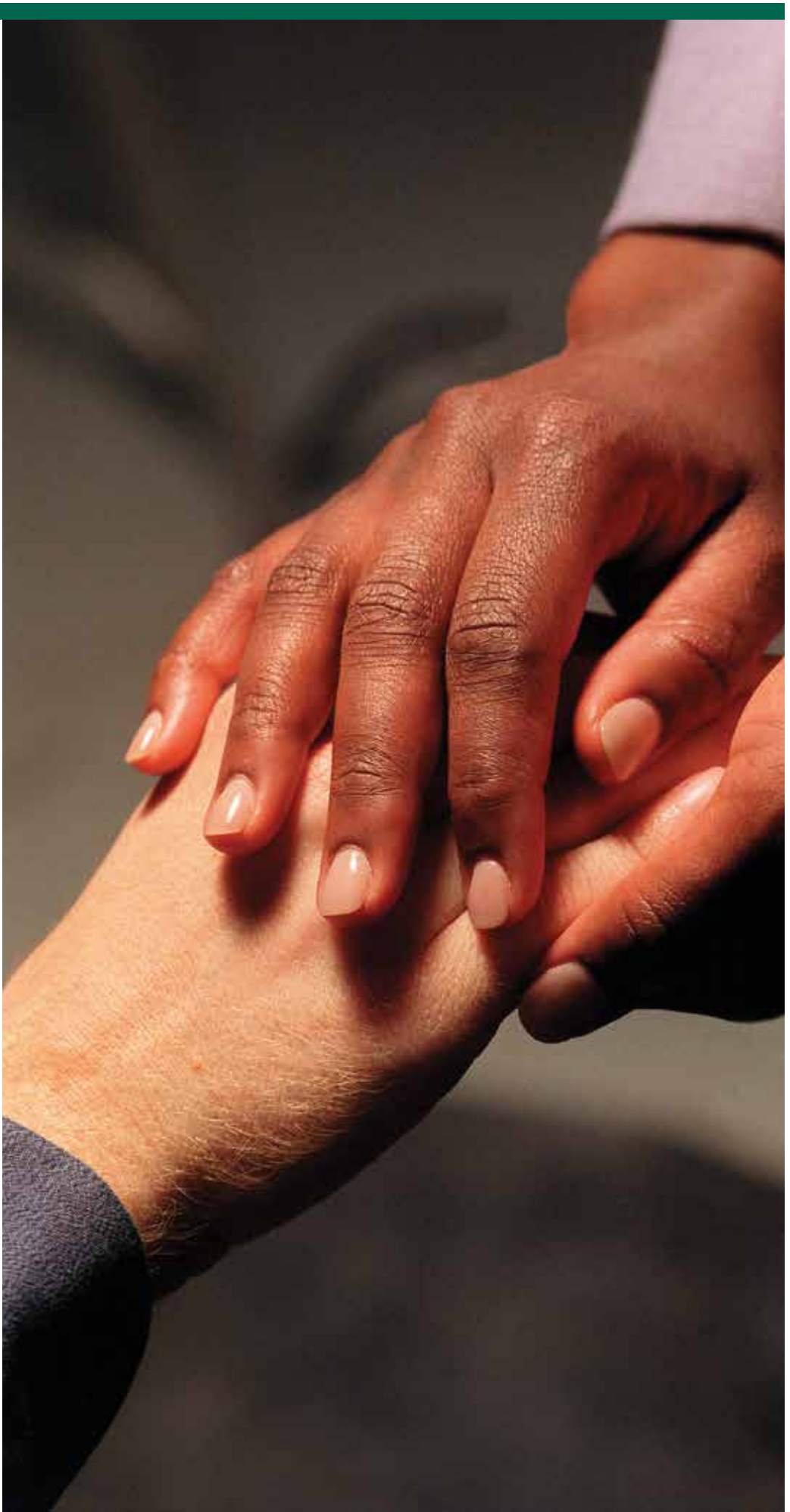

TABLE III. Products licensed in the U.S. to treat von Willebrand disease (MASAC recommendations #187)

A. Desmopressin formulations to treat type 1 and type 2 vWD

Product name	Manufacturer	U.S. Distributor	Formulation	Recommended dosage and administration
DDAVP injection	Ferring AB (Malmo, Sweden)	Aventis Pharma	For parenteral use (IV or SQ), 4 µg/mL in a 10-mL vial	1) 0.3 µg/kg, mixed in 30 mL normal saline solution, infused IV slowly over 30 minutes. May repeat after 24 hours. 2) 0.3 µg/kg by subcutaneous injection. May repeat after 24 hours. DO NOT USE IN CHILDREN UNDER THE AGE OF 2 YEARS OR IN PREGNANT WOMEN.
Stimate nasal spray for bleeding	Ferring AB (Malmo, Sweden)	CSL Behring	Nasal spray, 1.5 mg/mL. The metered dose pump delivers 0.1 mL (150 µg) per actuation. The bottle contains 2.5 mL with spray pump capable of delivering 25 150-µg doses or 12 300-µg doses.	In patients weighing <50 kg, give one spray in one nostril (dose = 150 µg). In those weighing >50 kg, give one spray in each nostril (dose = 300 µg). May repeat after 24 hours. DO NOT USE IN CHILDREN UNDER THE AGE OF 2 YEARS OR IN PREGNANT WOMEN

TABLE III. Products licensed in the U.S. to treat von Willebrand disease (MASAC recommendations #187)

B. Products derived from human plasma that contain factor VIII and von Willebrand factor

Product name	Manufacturer	Method of viral inactivation	Heparin in final vial (units/mL)	Specific activity of final product (IU factor VIII/mg total protein after addition of stabilizer)	Viral safety studies in humans with this product	Viral safety studies in humans with another product, but similar method	FDA approved for von Willebrand disease	Ratio of vWF: FVIII
Alphanate	Grifols	1. Affinity chromatography 2. Solvent/detergent (TNBP/Polysorbate 80) 3. Dry heat (80°C, 72h)	1.0	>5	No	Yes	Yes	0.4–1:1
Humate-P	CSL Behring GmbH (Marberg, Germany)	1. Pasteurization (60°C, 10 hrs)	None	1–2	Yes	No	Yes	1.8–2.8:1
Koate-DVI	Talecris	1. Solvent/detergent (TNBP/Polysorbate 80) 2. Dry heat (80°C, 72h)	None	9–22	No	Yes	No	Unknown

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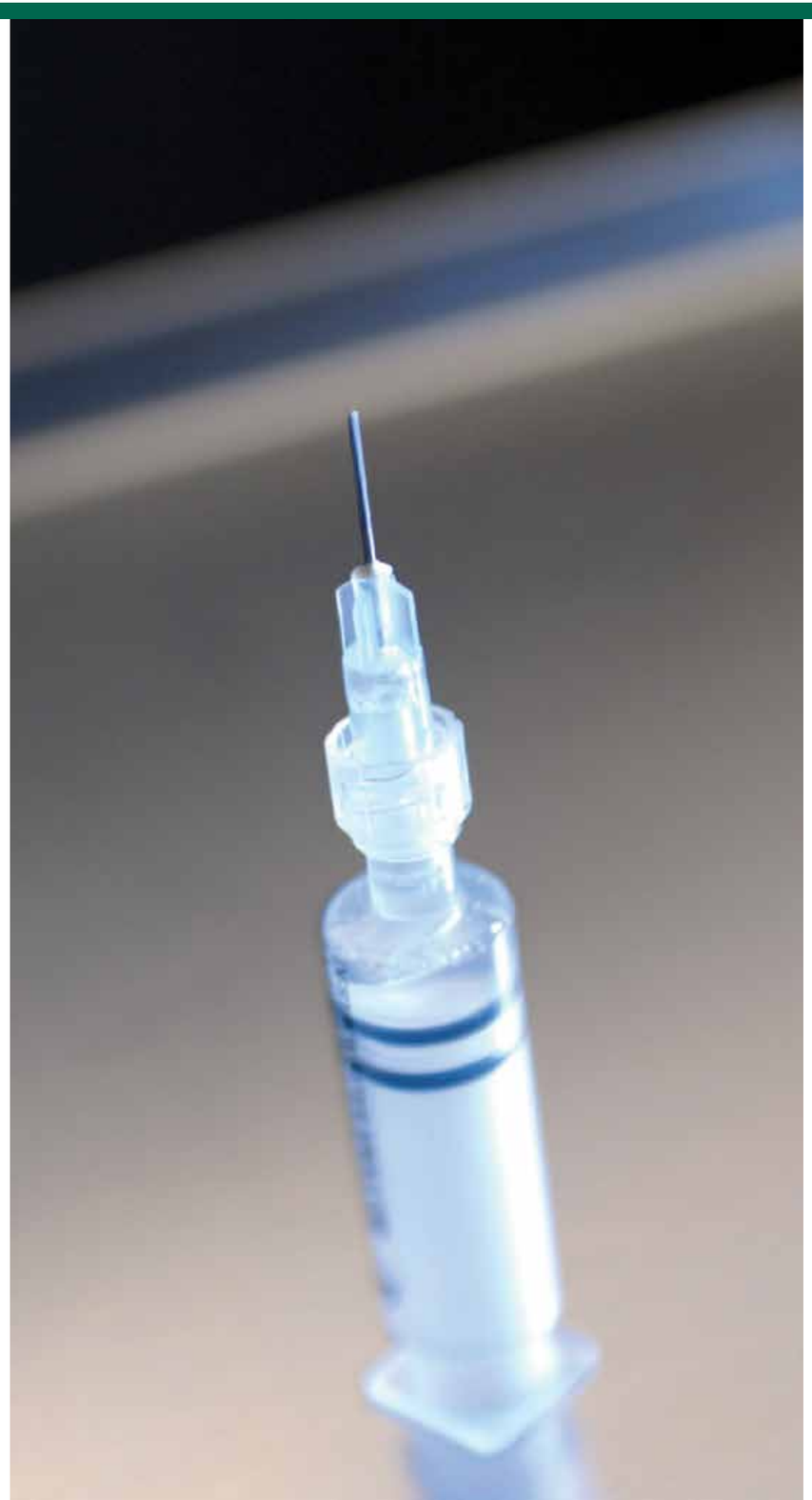

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IN GENERAL, FOLLOW THESE GUIDELINES:

- Do not keep this patient waiting.
- A bleeding episode requires immediate attention.
- Infuse promptly.
- Therapeutic infusions should precede radiographic studies, invasive procedures or complex evaluations.
- Listen to the patient.
- These patients are generally quite knowledgeable about the disease. Be prepared to work in collaboration with them.
- Contact the patient's hematologist.

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