TREATMENT OF HEMOPHILIA

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PROTOCOLS FOR THE TREATMENT OF HEMOPHILIA AND VON WILLEBRAND DISEASE

Third edition

Hemophilia of Georgia
Georgia, U.S.A.

WFH

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

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The *Treatment of Hemophilia* series is intended to provide general information on the treatment and management of hemophilia. The World Federation of Hemophilia does not engage in the practice of medicine and under no circumstances recommends particular treatment for specific individuals. Dose schedules and other treatment regimes are continually revised and new side effects recognized. WFH makes no representation, express or implied, that drug doses or other treatment recommendations in this publication are correct. For these reasons it is strongly recommended that individuals seek the advice of a medical adviser and/or consult printed instructions provided by the pharmaceutical company before administering any of the drugs referred to in this monograph.

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Treatment of Hemophilia Monographs
Series Editor
Dr. Sam Schulman

Preface from the WFH

The WFH believes it is important to provide examples of protocols used in various centres in the developed world. This is the protocol currently used by treaters in Georgia, U.S.A., and while direct references to Hemophilia of Georgia have been modified for an international audience, it reflects their circumstances. Treatment may be different in Buenos Aires, Rome, or Singapore. Any protocol that is put into practice must be developed by treaters in their given situation.

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Protocols for the Treatment of Hemophilia and von Willebrand Disease

Hemophilia of Georgia

Introduction

Hemophilia of Georgia, Inc., and the hemophilia treatment centres of Georgia have combined resources and expertise to develop guidelines for physicians who treat patients with hemophilia.

These protocols are meant to assist in providing quality standards of care for the management of hemophilia. They are not intended to replace regular evaluation and treatment by the hemophilia treatment centre. It is hoped that communication between the patient's private physician and the hemophilia centre will be enhanced by the existence of these guidelines.

These therapeutic approaches are based on the experiences of the advisors as well as protocols established by other hemophilia centres in the United States. Any treatment must be designed according to the needs of the individual and the resources available.

Hemophilia and Its Diagnosis

Hemophilia A and B are X-linked disorders caused by deficiencies of clotting factors VIII (FVIII) and IX (FIX) respectively. The frequency of FVIII deficiency is thought to be approximately one per 5,000-10,000 male births; for FIX deficiency, it is approximately one per 30,000-50,000 male births.

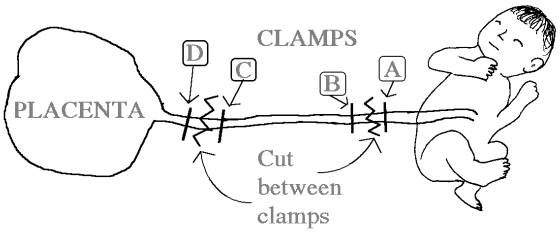
Early carrier detection is based on pedigree analysis, the measurement of the ratio of maternal FVIII coagulant activity to von Willebrand factor (VWF) and, more recently, DNA analysis. The maternal DNA-based diagnosis is the most accurate but is not informative in all patients. Prenatal diagnosis is possible by performing a chorionic villous biopsy at 9-11 weeks or an amniocentesis at 12-15 weeks gestation and extracting the DNA from fetal cells for DNA-based diagnosis. For further information regarding availability of testing resources, contact a hemophilia treatment centre.

Table 1: Clinical classifications of persons with either hemophilia A or hemophilia B

Severe hemophilia	Moderate hemophilia	Mild hemophilia
Generally < 1% factor level	Generally 1 to 5% factor level	6-40% factor level
Spontaneous bleeding characteristic	Can bleed with slight injury	Bleeding typically only with severe injury, surgery, invasive procedures
May bleed 1 to 2 times per week	May bleed 1 time per month	May never have a bleeding problem
Characterized by joint bleeding (hemarthrosis)	May have joint bleeding	Rarely has joint bleeding

Postpartum diagnosis of hemophilia A relies on the ability to detect low FVIII coagulant activity in a suspected newborn on cord blood (preferred) or a peripheral venous blood sample. The diagnosis of mild hemophilia B or FIX deficiency is more difficult because the newborn normally has low levels of FIX coagulant activity (a vitamin K dependent factor). Low levels of FIX may exist for up to six months in a child who does not have hemophilia. Arterial, jugular, femoral, and antecubital punctures, as well as circumcision or other invasive procedures, are contraindicated until a diagnosis is obtained and the patient is treated beforehand to achieve an adequate factor level.

Figure 1: Suggested technique for collection of cord blood by obstetricians to avoid venipuncture of newborn (for FVIII assay)



Immediately after delivery, place clamps in order A through D. Cut the cord as shown and obtain blood from freed section.

Treatment for Bleeding Episodes

Basic principles of treatment

1. Treat bleeds early with factor replacement therapy, i.e., within two hours of the onset of symptoms. Do not wait for the appearance of physical signs.

    a) Treat a suspected intracranial hemorrhage immediately.

    b) Patients, even young children, can recognize joint hemorrhage early in its course. Early recognition and treatment will limit tissue damage. In addition, less factor is ultimately needed and activities are not interrupted.

    c) **If in doubt, treat**. If a person with hemophilia has sustained an injury or if he thinks he may be bleeding, treat first and perform diagnostic tests later.

2. Treat veins with care. The veins are the lifelines for persons with hemophilia.

    a) 23- or 25-gauge butterfly needles are recommended.

    b) Never cut down, except in a dire emergency; a cut-down destroys veins.

    c) After venipuncture, apply pressure with one or two fingers for three to five minutes.

3. Avoid products that cause platelet dysfunction, especially those containing acetylsalicylic acid (Aspirin®). (See Appendix, page 14.) Non-steroidal anti-inflammatory agents should be used with caution. We recommend acetaminophen with or without codeine for pain control. When using multiple medications, be aware of their potentially hazardous interactions. When a patient with a bleeding disorder requires anticoagulation for problems such as deep vein thrombosis or myocardial infarction with stent placement, correct the hemostatic defect and use anticoagulants or antiplatelet agents as per *Chest* guidelines.

4. Home therapy with clotting factor is usually begun when a child is three to five years old. The benefits include reduction of costs and complications of hemophilia. The child should be encouraged to participate in his own infusion at an early age. Many hospitals allow patients to bring their own factor for infusion in the emergency room.

5. The concept of comprehensive care at a hemophilia treatment centre is a state-of-the-art approach to hemophilia treatment. In this setting, the patient is evaluated by a multidisciplinary team that usually consists of a hematologist, orthopedist, nurse coordinator, social worker, and physical therapist, and may also include a dietician, infectious disease specialist, hepatologist, dentist, occupational therapist, vocational

rehabilitationist, psychologist, and genetics counsellor. This team devises a coordinated care plan for the patient and relies on his private physician for follow-up.

Communication between the patient's private physician and the hemophilia treatment centre is essential for optimal management.

Options available for the treatment of a person with factor VIII deficiency (hemophilia A)

Factor VIII concentrates
Commercially prepared, lyophilized FVIII is distributed under a variety of brand names. Since the mid-1980s, new products have been introduced which have undergone viral attenuation. These products fall into three categories:

- Recombinant products;
- Monoclonal antibody purified products; and
- Intermediate and high purity FVIII products (which are also used for von Willebrand disease).

Consult the product insert guide for specific instructions. Hemophilia of Georgia does not endorse one particular brand.

There may be specific product recommendations for patients with complications such as inhibitors or human immunodeficiency virus (HIV) infection. Recombinant activated factor VIIa (FVIIa) is licensed for the treatment of bleeding in patients with inhibitors to FVIII or FIX. The standard dose is 90 mcg/kg given every two to three hours until hemostasis is achieved or until treatment is thought to be ineffective. Consult a hemophilia treatment centre at the initiation of therapy if the patient has a problem more complicated than a simple bleed.

a) Vials are available in dosages ranging between approximately 250 to 3,000 units each.

b) **Each FVIII unit per kilogram of body weight infused intravenously will raise the plasma FVIII level approximately 2%. The half-life is approximately 8 to 12 hours. A calculated dose should be verified by measuring the patient's factor level.**

c) The formula for calculating the dosage for FVIII is taking the patient's weight in kilograms and multiplying the factor level desired times 0.5, which will indicate the number of factor units required.
Example: 45 kg X 40 (% level desired) X 0.5 = 900 units of FVIII

Refer to the chart on page 13 for suggested factor level and dosage based on type of hemorrhage.

d) **FVIII should be infused by slow IV push at a rate not to exceed 3 mL per minute in adults and 100 units per minute in young children.**

e) **Always give the entire content of each vial of FVIII even if that exceeds the calculated dosage. Factor is expensive and should not be wasted.**

f) Continuous infusion of FVIII should be supervised by an experienced hematologist. A 50 unit/kg bolus followed by 4-5 units/kg per hour of FVIII will provide a FVIII level of approximately 100% in a patient with severe hemophilia A. Daily factor levels must be monitored. FVIII concentrates are stable in IV solutions for at least 12 hours at room temperature. Therefore, 12-hour bags of factor concentrate for continuous infusion may be prepared by the pharmacy and administered without concern for proteolytic inactivation, degradation, or bacterial contamination.

Cryoprecipitate
Cryoprecipitate should not be used to treat hemophilia A. Standard preparations of cryoprecipitate have not undergone viral attenuation and are not recommended. The average FVIII content per bag is 60-100 units.

DDAVP
DDAVP, a synthetic vasopressin analogue, and Stimate® (the intranasal form of DDAVP) are useful in the treatment of persons with mild hemophilia who have a 5% or greater FVIII level and have been shown through pre-testing to be responsive to its infusion.

DDAVP releases stored FVIII complexed with VWF into the circulatory system and increases the FVIII level two to three times, which is often sufficient to provide hemostasis for minor bleeding episodes. The advantage of this product is that it reduces or avoids the exposure to blood products. Prior to therapeutic use, DDAVP should be evaluated as follows:

- Measure the factor level pre-infusion;
- Infuse DDAVP (0.3 mcg/kg of body weight diluted in 30-50 cc of normal saline) slowly, over a 15-30 minute period; and
- Measure the factor level 30-60 minutes post-infusion.

Stimate® is 15 times more concentrated than the standard intranasal DDAVP used for treating diabetes insipidus and enuresis. Rx: one spray in a single nostril for children over the age of five and under 50 kg and one spray in each nostril for patients weighing over 50 kg. Because of marked variability in response to intranasal Stimate®, all patients should be tested before therapeutic use. As with IV DDAVP, the use of Stimate® should be limited, if possible, to one daily dose to prevent exhaustion of storage pools of factor VIII. Fluid restriction to 3/4 maintenance fluids is important and the serum sodium must be monitored during periods of repetitive daily use of DDAVP or Stimate®. Additionally, the patient should be instructed to return to the clinic if there are symptoms of severe headache, weakness, or vomiting. Contemplative use of DDAVP that exceeds a single dose should be discussed with a physician familiar with the use and complications of this medication.

Antifibrinolytic agents

a) Epsilon-aminocaproic acid (EACA) is an antifibrinolytic agent that can be used along with factor VIII products for invasive dental work or for the treatment of mouth bleeds. It is not recommended for treatment of renal bleeding. The dose is 50-100 mg/kg (maximum 6 grams) every four to six hours for seven to ten days (maximum 24 grams per 24 hours). A liquid preparation is available and a mouthwash can be prepared.

b) Tranexamic acid (TECA or TA) is another antifibrinolytic agent but not readily available in the U.S., and it is only available in a parenteral form. A dose of 25 mg/kg orally every 8 hours for 10 days is often required to inhibit fibrinolysis and allow wound healing. Tranexamic acid may be preferred since a lower dose is required and it may be less expensive than EACA.

Options available for the treatment of a person with factor IX deficiency (hemophilia B)

Factor IX concentrates

Commercially prepared, heat-treated, lyophilized FIX concentrates from plasma are distributed under a variety of brand names. Since 1991, new products have been introduced which have undergone viral attenuation. These products fall into two classes:

- Pure coagulation FIX products; and
- FIX complex concentrates, which are currently unavailable in the U.S.

Also available is a recombinant FIX product. Consult the product insert guide for specific instructions. Hemophilia of Georgia does not endorse a particular brand. There may be specific product recommendations for patients with HIV infection. Consult a hemophilia treatment centre for these recommendations.

The pure coagulation FIX products are thought to be largely free of the risks of thrombosis and complications related to disseminated intravascular coagulation (DIC).

a) Vials are available in dosages ranging between approximately 250-1,000 units each.

b) **Each FIX unit per kilogram of body weight infused intravenously will raise the plasma FIX level approximately 1%. The half-life is about 18 to 24 hours.** Due to a decreased recovery of factor, Benefix® requires approximately 20-50% more product to achieve the same peak level, though some children require higher amounts. Accordingly, 1.2 units/kg in adults and 1.5 units/kg in children will raise the FIX level by 1%.

c) The formula for calculating the dosage for plasma FIX is taking the patient's weight in

kilograms and multiplying by the factor level desired, which will indicate the number of factor units required.
Example: 45 kg X 40 (% level desired) = 1800 units of FIX

Refer to the chart on page 13 for suggested factor level and dosage based on type of hemorrhage.

d) **FIX should be infused by slow IV push at a rate not to exceed a volume of 3 ml per minute.**

e) Continuous infusion of purified FIX concentrates should be supervised by an experienced hematologist.

Fresh frozen plasma (FFP)
FFP should not be used for these patients unless faced with a life-threatening emergency and only if FIX products are not available. However, FIX levels above 15%-20% are difficult to achieve. 15 - 20 ml/kg FFP (1 litre in adults) is an acceptable starting dose.

Antifibrinolytic agents
Antifibrinolytic agents, either as primary or adjunctive therapy, are recommended for treating patients with FIX deficiency who are treated with plasma or recombinant-derived FIX, similar to previous suggestions for use in factor VIII deficient patients.

Specific hemorrhages

Joint hemorrhage
a) First give the patient the appropriate dose of factor concentrate and then evaluate. X-rays may or may not be indicated.

b) Raise the factor level to 40-50% with first symptoms or after trauma. (Refer to previous explanations about calculations.) For a more significant joint hemorrhage, a bleed in a target joint, or joint bleeding in children, raise the level to 80-100% and call a hemophilia treatment centre.

c) A second infusion to raise the factor level to 40-50% may be required in 12 to 24 hours (hemophilia A) or in 24 hours (hemophilia B) and a third infusion in 72 hours if symptoms persist (i.e., if swelling and/or pain is not significantly improved), or the patient is a child or has a target joint.

d) The so-called "target joint bleeding" protocol where the patient receives 80-100% correction on the day of the bleed, and 40-50% correction on day one and three post-bleed, can be beneficial for many patients including children and those with target joints. Its use should be encouraged.

e) Immobilize the joint as soon as possible until pain subsides. A cryocuff is most helpful.

f) Adjunctive care: ice, temporary rest, and elevation.

g) Seek consultation at a hemophilia treatment centre if symptoms persist beyond three days or if a fracture is suspected.

h) Pain control: Aspirin®-free medication. (See Appendix, page 14.)

Muscle hemorrhage
a) First give the patient the appropriate dose of factor concentrate and then evaluate.

b) Raise the factor level to 40% with first symptoms or after trauma. Occasionally, more severe muscle hemorrhages require higher dosing of factor to a level of 80-100% as described above for treatment of joint bleeding. (Refer to previous explanations on page 3 or 5 about calculations.)

c) A second infusion with factor to raise the factor level to 40-50% is often required within 24 hours. The patient should be monitored for neurovascular compromise.

Iliopsoas hemorrhage
a) This is a form of muscle hemorrhage with unique presentation. This type of problem often presents as an acute abdomen or as hip pain. Signs may include pain in the lower abdomen, groin, and/or lower back, and pain on extension, but not on rotation, of the hip joint. There may be paresthesia in the medial aspect of the thigh or other signs of femoral nerve compression.

b) Immediately raise the factor level to 80-100%. Maintain factor levels above 50% for both hemophilia A and B for 48 to 96 hours, as symptoms dictate. Often, prolonged periods of factor use are needed as well as consideration of continuous infusion of factor.

c) Hospitalize for observation. Treat anemia as needed.

d) An imaging study, e.g., computed tomography (CT) scan, will confirm the diagnosis of an iliopsoas hemorrhage and help differentiate from acute appendicitis, for which this condition is often mistaken.

e) Limit activity until pain resolves. Physical therapy is helpful to restore full range of motion. **Refer to a hemophilia treatment centre.**

Central nervous system (CNS) hemorrhage / head trauma

a) Treat all post-traumatic head injuries and significant headaches as a head bleed. Raise factor level immediately to 80-100%. Do not wait for further symptoms to develop or for laboratory or radiological evaluation.

b) **This is a true medical emergency. Treat presumptively before evaluating.** Immediately raise factor level to 80-100% when CNS symptoms or significant trauma occur. If a hemorrhage has occurred, maintain at least a 50% factor level until the hemorrhage has improved (usually two to three weeks) with an objective head imaging study performed. Consult the hemophilia treatment centre for further recommendations once the patient has been stabilized. These patients will often go on long-term prophylaxis.

c) This requires immediate medical evaluation and hospitalization for observation. A CT scan or magnetic resonance imaging (MRI) should be performed.

d) In the case of a CNS bleed, refer to a hemophilia treatment centre.

e) In the case of suspected head trauma, first treat the patient with factor concentrate and then evaluate.

f) Severe headache may be a manifestation of HIV-related opportunistic infection. (See HIV issues, page 10.)

Throat and neck hemorrhage and severe tonsillitis

a) **This is a true medical emergency. Treat presumptively before evaluating.** Immediately raise factor level to 80-100% when symptoms or significant trauma occur. Maintain at least a 50% factor level for one to two weeks until the hemorrhage resolves. Consult the hemophilia treatment centre for further recommendations once the patient has been stabilized.

b) Trauma or symptoms of hemorrhage usually require hospitalization or follow-up by a hematologist and an otolaryngologist. A CT scan or MRI should be performed.

c) To prevent hemorrhage with severe tonsillitis, treatment with factor may be indicated in addition to culture and treatment with antibiotics.

Acute gastrointestinal (GI) hemorrhage

a) First give the patient the appropriate dose of factor concentrate and then evaluate.

b) Immediately raise the factor level to 80-100%. Maintain at least a 50% factor level until the etiology is defined.

c) Medical evaluation and possibly hospitalization are required for signs of GI bleeding and/or acute abdomen.

d) Treat anemia or shock as needed.

e) Treat origin of hemorrhage as indicated.

f) EACA or tranexamic acid may be used as adjunctive therapy as long as the possibility of concomitant renal bleeding has been eliminated. Consult a hemophilia treatment centre for recommendations.

Acute abdominal hemorrhage

a) Acute abdominal hemorrhage can mimic a number of infectious conditions and appropriate radiological studies are often necessary. Iliopsoas hemorrhage should be ruled out. (See Iliopsoas hemorrhage, page 5.)

b) Immediately raise the factor level to 80-100%. Maintain at least a 50% factor level until the etiology can be defined. Consult the hemophilia treatment centre for recommendations.

Ophthalmic trauma or hemorrhage

a) First give the patient the appropriate dose of factor concentrate and then evaluate.

b) Immediately raise the factor level to 80 to 100%. Maintain a factor level of at least 50%.

c) An evaluation by an ophthalmologist and a hematologist is required with symptoms or signs of trauma/hemorrhage.

Renal hemorrhage

a) Avoid use of antifibrinolytic agents.

b) Painless hematuria should be treated with complete bed rest and vigorous hydration (1-1/2 times maintenance) for 48 hours.

c) If there is pain or persistent gross hematuria, give factor to raise the level to 50%.

d) Evaluate if hematuria (gross or microscopic) persists or if there are repeated episodes. Prednisone (1 mg/kg x 3-5 days) could be used, though the benefit is unclear.

Oral hemorrhage

a) Bleeding may be controlled with EACA or tranexamic acid alone, or with factor and either EACA or tranexamic acid, if bleeding is prolonged, significant, or difficult to control. A mouthwash can be prepared using EACA. Treatment of a frenulum bleed in infants often requires treatment with factor replacement to at least 50% for several days.

b) Evaluate and treat for anemia as indicated.

c) The application of topical agents such as Avitene® or thrombin on the bleeding mucous membrane may be effective. Ice in the form of popsicles may also be effective. A soft, cold diet for 24 hours is recommended.

d) Consult a hematologist, a dentist, or an otolaryngologist as indicated.

e) A custom fit mouth piece might be helpful to provide local compression.

Epistaxis

a) Factor replacement therapy is usually not required because the formation of a platelet plug often is adequate.

b) Have the patient place his head forward to avoid swallowing blood and have him gently blow out weak clots. Apply firm pressure to the fleshy part of the nose for at least 10 to 20 minutes.

c) For bleeds related especially to allergies, upper respiratory tract infections (URI) or seasonal changes, try Neo-Synephrine® 0.5-1%, two drops in each nostril b.i.d. for 5 days. The use of a cold mist vaporizer may also be helpful.

d) Watch for anemia if bleeding is prolonged or occurs frequently.

e) Ear, nose, and throat (ENT) consultation may be indicated; 4% cocaine solution may be advised.

f) The use of EACA or tranexamic acid may be helpful.

g) The use of intranasal normal saline solution or gel may be helpful.

h) Nose clips might be helpful to keep pressure applied for 10-20 minutes.

Soft tissue hemorrhage

a) Most superficial soft tissue bleeding does not require factor replacement therapy. The application of firm pressure and ice may be helpful.

b) Evaluate for severity and possible muscular or neurovascular involvement. Rule out the possibility of trauma to spaces containing vital organs, such as the head or abdomen. Open compartmental hemorrhage, such as in the retroperitoneal space, scrotum, buttocks, or thighs, can result in extensive blood loss. If this is suspected, treat with factor to 80-100% immediately.

c) A young, active child with hemophilia commonly has numerous bruises. Parents are sometimes wrongfully accused of child abuse.

Lacerations and abrasions

a) Superficial lacerations can be treated by cleaning the wound followed by application of pressure and steri-strips.

b) Abrasions require cleaning and pressure.

c) Deep lacerations require raising the factor level to 50%, then suturing. Removal of sutures usually requires another infusion of factor.

von Willebrand disease

von Willebrand disease (VWD) is the most commonly inherited bleeding disorder. Unlike hemophilia, which is X-linked and usually affects only males, VWD is generally inherited on an autosomal basis and is likely to affect females as commonly as males. The disease is due to a reduction or abnormality of a glycoprotein (called von Willebrand factor [VWF]) in the blood that is necessary for adhesion of the platelet to the vessel wall. Because this protein also serves as the carrier protein and stabilizer of FVIII, FVIII activity in the blood is sometimes decreased in proportion to the reduction in measurable VWF.

Symptomatic individuals with VWD will usually present with mucosal bleeding (e.g., epistaxis, heavy menses, oral, GI or genitourinary (GU) bleeding, or easy bruising). Menorrhagia (heavy menses) is a common problem for women with this bleeding disorder. Hormonal therapy with various forms of estrogen replacement may help, as will consultation with gynecology. DDAVP and antifibrinolytic agents may also help. In rare cases, some people with VWD experience the joint and muscle bleeding frequently observed in people with hemophilia. Surgical bleeding is usually immediate and if corrected, does not manifest the delayed bleeding seen in people with hemophilia. Coordination of all surgery with the hemophilia treatment centre is recommended.

Several types of VWD have been identified. Patients with Type 1 VWD have both the most common and mildest form of the disorder. They have reduced levels of VWF, but its structure and function appear to be normal. Patients with Type 2 VWD have varying levels of VWF, but the protein does not function properly, manifested by a lower functional activity (ristocetin cofactor). There are several variants of Type 2; the most important to distinguish is Type 2B because of possible treatment complications if DDAVP were utilized (see below). Type 3 VWD patients are severely affected because they have an absence of VWF and concomitant reduction in circulating FVIII—these patients may behave like those with moderate hemophilia. This type of VWD should be diagnosed and treated only by a hematologist who specializes in VWD and hemophilia.

Bleeding patients with Type 1 VWD can generally be treated with DDAVP (see page 3); some patients with Type 2A may also respond to its use. Those with Types 2B, 2N, 2M, or 3 disease who are bleeding cannot be treated with DDAVP; Type 2B patients may develop platelet clumps with resultant thrombocytopenia when treated with DDAVP, and Type 3 patients will not increase their VWF in response to DDAVP. The appropriate treatment for patients with these types of VWD is a FVIII concentrate rich in VWF. The concentrate currently available with the highest concentration of VWF is called Humate P® (Haemate P®). Other FVIII concentrates that contain substantial amounts of VWF are Alphanate SD® and Koate DVI®. All of these concentrates are made from plasma screened for HIV and hepatitis viruses and are treated to inactivate viruses that might escape detection. The use of these products is explained on page 3. Highly purified FVIII concentrates—monoclonal and recombinant—cannot be used to treat VWD because they lack VWF.

Cryoprecipitate, which is screened for viruses but not treated to inactivate them, is also rich in VWF. Because it is likely to be less safe than the viral-attenuated concentrates, its use is not recommended unless a concentrate is not available. Any VWF-rich concentrate (see above) can be used to treat patients with Types 1 and 2A if DDAVP is either not available, or its use gives an inadequate clinical response or is poorly tolerated by the patient.

Other Management Issues

Dental

1. Routine examinations and cleaning generally can be performed without raising the factor level. Adequate coverage (i.e., factor concentrate or antifibrinolytic therapy) should be given prior to and possibly after the dental appointment in those patients who need deep cleaning or have heavy plaque and/or calculus accumulation where bleeding would be induced with scaling. Factor should always be given prior to dental procedures where block local anesthesia is indicated. In mild and some moderate patients, infusion of factor may not be necessary prior to restorative work if only local infiltration of anesthesia is going to be used.

2. Raise the factor level to at least 50% prior to giving a mandibular block. Local anesthesia is not contraindicated for hemophilia patients. Nitrous oxide and/or IV analgesia may be used in addition to local anesthesia.

3. Dental extractions require a prior infusion of factor concentrate that raises the level to 50-100%. Antifibrinolytic products should be used concomitantly with factor concentrates or DDAVP. The dose for EACA, started prior to the procedure, is 50-100 mg/kg every 4-6 hours, for 7-10 days (maximum 24 grams per 24 hours). The dose for tranexamic acid is 25 mg/kg orally every 8 hours for 10 days. Unless contraindicated, we generally recommend the use of antifibrinolytic agents until the sutures are removed and the wound is healed.

4. When primary teeth are exfoliating, bleeding may occur. Pressure and ice should be used as a first attempt to control bleeding. If this is ineffective, begin EACA therapy. In rare instances, factor may need to be administered. For patients with a history of prolonged bleeding, it may be appropriate for the dentist to extract the tooth with proper factor infusion.

5. Extensive procedures may require hospitalization for proper dental/medical management; i.e., procedures requiring sutures, multiple extractions, etc.

6. The position of the third molars (wisdom teeth) should be evaluated during the teenage years. Early extraction should be considered in order to prevent complications or a more extensive surgical approach when older. We usually recommend infusion of factor concentrate for several days after wisdom teeth extractions.

7. Avitene® and/or gel foam pre-soaked in topical thrombin solution can be used as a hemostatic agent in the extraction site or on oozing gingiva. When possible, primary closure is desirable.

8. The above recommendations are general guidelines. Each patient should be evaluated on an individual basis according to the severity of his condition. A consultation with a hematologist familiar with the patient is recommended.

9. Patients with inhibitors require close collaboration with a hemophilia treatment centre hematologist.

Surgery

1. Management of the surgical patient is best undertaken at a hemophilia treatment centre. The institution undertaking such procedures must be capable of performing a factor inhibitor screen prior to the scheduled surgery and measurement of serial factor levels during the surgical procedure.

2. Operative and invasive procedures can be performed once the coagulation defect is

corrected by infusion with factor. Consultation with a hematologist familiar with hemophilia is necessary.

3. The patient's individual response to the replacement material should be documented prior to surgery. (If the patient does not respond adequately, rule out an inhibitor. See Factor inhibitor, page 10.) Immediately prior to the procedure, raise the calculated factor level to 80-100%; maintain at least a 50% level for 1-2 weeks, depending on the type of surgery. Continuous infusion therapy may be preferable for the management of surgical patients when factor concentrates with data of stability for continuous infusion are available. Factor levels should be monitored at least daily during continuous infusion.

4. Maintain an appropriate factor level for 5-7 days for minor surgery; 10-14 days for major surgery; and prophylaxis 3-4 times a week for up to 6 weeks for orthopedic procedures during rehabilitation.

Minor invasive procedures

Factor should be infused before invasive diagnostic procedures—such as lumbar puncture, arterial blood gas determination, bronchoscopy, liver biopsy or endoscopy with brushings, or biopsy.

Immunizations

1. Follow the routine schedule for children, but give injections subcutaneously instead of intramuscularly to avoid muscle hemorrhage. Apply direct pressure to the site of the injection for five minutes.

2. Immunocompromised patients should not receive live viral vaccines where the risk of infection outweighs complications of the vaccine. Do not give the oral polio vaccine.

3. Persons with HIV should be given pneumococcal and annual influenza vaccines.

4. The hepatitis A and hepatitis B vaccine series should be given to all newly diagnosed patients and to those indicating no exposure to either hepatitis A or hepatitis B virus. Family members involved in factor replacement therapy in the home who test negative should also receive the series. Vaccines can be given subcutaneously in the thigh or over the deltoid area (the deltoid is preferable). Consult the package insert for the specifics of administration to persons with hemophilia. Antibody to hepatitis B virus should be determined following the full immunization schedule to ensure immunity.

Sports and hemophilia

1. Sports activities should be encouraged to promote muscle strengthening and increased self-esteem. Choice of sports should reflect an individual's preference, ability, and physical condition.

2. Low-impact activities, such as swimming and golf, should be encouraged. High-contact sports, such as football and wrestling, are not advised. The patient should consult with a physician before engaging in sports activities to discuss appropriateness, protective gear, and prophylaxis prior to the activity.

Complications of Hemophilia

Factor inhibitor: IgG antibodies to factors VIII and IX

An inhibitor should be suspected if the patient does not respond to the usual dose of factor. The previous guidelines in these protocols do not apply to patients with inhibitors. Management of this difficult problem must be coordinated with the expertise of a hematologist who specializes in bleeding disorders.

Synovitis

1. The clinical findings are a grossly distended (but not tense or painful) joint, usually the knee.

2. Synovitis may mimic an acute bleed. If hemorrhage is ruled out, treatment with a non-steroidal, anti-inflammatory drug (NSAID) may be used, but the patient should be warned about the potential for increased bleeding. Cox-2 inhibitor non-steroidals may have less potential for

bleeding. Chronic use of NSAIDs should be limited and closely supervised by a physician who understands their risks and benefits and knows how to calculate a dose that is appropriate for the patient's age, renal function, and risk of cardiovascular disease. Do not use Aspirin®-containing medications. Refer the patient for multidisciplinary evaluation at a hemophilia treatment centre.

3. This problem is difficult to manage and is best handled with a team approach, specifically by the hematologist, orthopedist, and physical therapist at the hemophilia treatment centre.

HIV

1. Many persons with hemophilia who were treated with plasma-derived factor prior to 1985 are HIV seropositive. Most persons with hemophilia are aware of their serostatus, although some are reticent to discuss their HIV infection. Consequently, healthcare providers should be aware of the probability of HIV infection in a person with hemophilia born before 1985. A significant percentage of HIV-infected individuals with hemophilia have survived more than two decades with this blood-borne infection and are clinically doing very well. Although the manifestations of the opportunistic infections seen with HIV infection are protean and beyond the scope of this document, clues to the presence of progressive HIV infection and common presenting problems of HIV-infected persons include:
   - unexplained fever
   - anorexia/weight loss/wasting
   - pharyngitis or odynophagia
   - significant periodontal disease
   - oral candidiasis
   - headaches (which may be a manifestation of meningitis)
   - recurrent sinusitis
   - seborrheic dermatitis or other chronic dermatoses
   - history or presence of herpes zoster
   - pneumonia
   - chronic diarrhea
2. Causes of pneumonia in this setting include *Pneumocystis carinii* (PCP), common bacterial pathogens, mycobacteria, fungi, and a variety of uncommon organisms. If pulmonary tuberculosis is suspected, appropriate isolation precautions should be instituted.
3. Thrombocytopenia can be a complication of HIV infection and can cause bleeding independent of the clotting disorder seen in patients with hemophilia.
4. Plasma-derived factor concentrates available since 1985 and the new recombinant products have virtually eliminated the risk of HIV infection. **Therefore, patients born after 1985 are most likely at no increased risk for HIV infection unless there are other risk factors.** Routine serologic screening of source plasma, viral inactivation procedures, and the development of recombinant products are responsible for this important advance.
5. For the rare person with hemophilia whose HIV serostatus is unknown, voluntary, confidential testing and pre- and post-test counselling are available through comprehensive hemophilia centres. HIV risk reduction counselling may also available.
6. If a healthcare worker sustains a significant exposure to blood or body fluids from a patient with hemophilia, the potential for transmission of blood-borne pathogens should be considered. In addition to having HIV infection, many persons with hemophilia also have chronic hepatitis C (HCV) infection and a few have chronic hepatitis B (HBV).

Hepatitis C

1. Most persons with hemophilia who received clotting factor before 1990 acquired HCV infection. Almost all persons with hemophilia who have an HIV infection have HCV co-infection. HCV infection causes chronic hepatitis in > 80% of cases and can lead to cirrhosis and liver cancer.

2. Although HCV is more readily transmitted by blood exposure than HIV, sexual transmission of HCV is uncommon.

3. Alcohol consumption can accelerate the progression of HCV liver injury and its use should be discouraged.

4. Persons with chronic HCV are more susceptible to the hepatotoxic effects of other drugs.

5. Persons with chronic HCV can have a more severe illness should they contract hepatitis A or B; consequently, persons with HCV infection should be screened for hepatitis A and B and offered vaccine should they be non-immune.

6. Although treatment of HCV has side effects, selected patients may benefit from therapy with a combination of pegylated interferon and ribavirin. Most patients with hemophilia can, with clotting factor infusion, safely undergo liver biopsy to help stage hepatitis C and assess the need for antiviral therapy. Liver biopsies should be performed at a referral centre with expertise in managing clotting factor infusion.

Allergic reactions to factor replacement products

1. To avoid the possibility of reaction, use the filter included in the factor package.

2. Antihistamines such as Benadryl® (and on rare occasions, steroids) may be used to prevent or reduce symptoms.

3. Sometimes, changing factor brand may reduce symptoms.

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Appendix 1

Desired Plasma Factor Level and Dosage for Bolus Infusions

Type of Hemorrhage	Hemophilia A (VIII)		Hemophilia B (IX)	
	Desired Level	Dose (Units/Kg)	Desired Level	Dose* (Units/Kg)
Joint				
• Adults	40-50%	20-25	40-50%	40-50
• Children	80-100%	40-50	80-100%	80-100
Muscle (except iliopsoas)	50%	25	50%	50
Iliopsoas				
• Initial	80%–100%	40–50	80%–100%	80–100
• Maintenance	>50%	25**	>50%	50***
CNS/head				
• Initial	80%–100%	40–50	80%–100%	80–100
• Maintenance	>50%	25**	>50%	50***
Throat and neck				
• Initial	80%–100%	40–50	80%–100%	80–100
• Maintenance	>50%	25**	>50%	50***
Gastrointestinal				
• Initial	80%–100%	40–50	80%–100%	80–100
• Maintenance	50%	25**	50%	50***
Ophthalmic				
• Initial	80%–100%	40–50	80%–100%	80–100
• Maintenance	>50%	25**	>50%	50
Renal	50%	25	50%	50
Deep laceration	50-100%	25-50	50-100%	50-100
Surgery				
• Initial	80%–100%	40–50	80%–100%	80–100
• Maintenance	50%	25**	50%	50***

* For recombinant FIX, multiply x 1.2 for adults and 1.5 for children

** In general, maintenance doses for hemophilia A are given every 12 hours. This may need to be modified according to the individual patient's half-life.

*** In general, maintenance doses for hemophilia B are given every 24 hours. This may need to be modified according to the individual patient's half-life.

Appendix 2

Common Preparations Containing Aspirin®

Acuprin 81 (Richwood)
Aggrenox Capsules (Boehringer-Ingelheim)
Alka Seltzer Plus Cold (Bayer)
Alka Seltzer w/Aspirin (Miles)
Anacin (Whitehall)
Arthritis Pain Formula (Whitehall)
Ascripton (Rhone-Poulenc Rorer)
Aspergum (Schering-Plough)
Azdone (Central)
B-A-C (Mayrand)
Bayer (Glenbrook)
Bayer Childrens (Glenbrook)
B-C Cold-Sinus-Allergy Powder (Block)
B-C Powder (Block)
B-C Tablets (Block)
Bufferin (Bristol-Myers)
Cama (Sandoz)
Carisoprodol Compound (Various)
CVS Aspirin (CVS Pharmacy)
Darvon Compound-65 (Lily)
Damason-P (Mason)
Disalcid Capsules and Tablets(3M)
Doans (Novartis)
Dristan (Whitehall Robins)
Easprin (Parke Davis)
Ecotrin (Smithkline Beecham)
Empirin (Burroughs Wellcome)
Endodan Tablets (Endo Generics)
Empirin w/Codeine (Burroughs Wellcome)
Equagesic (Wyeth)
Excedrin (Bristol-Myers)
Fiorinal (Sandoz)
Fiorinal w/Codeine (Sandoz)
Fiortal with Codeine Capsules (Geneva)
Gelprin (Alra)
Genprin (Goldline)
Goody's (Goody)
Halfprin (Kramer)
Helidac Therapy (Prometheus Labs)
Kaopectate (Pharmacia)
Lobac Capsules and Tablets (Sealtrace)
Magan Tablets (Savage)
Methocarbamol & Aspirin Tablets (PAR)
Magsal Tablets (U.S. Pharmaceutical)
Mono-Gesic Tablets (Schwarz)
Lortab ASA (Whitby)
Magnaprin (Rugby)
Methocarbamol w/ASA (Various)
Midol (Bayer)
Norgesic (3M)
Norgesic Forte (3M)
Norwich Aspirin (Chattem)
Oxycodone w/Aspirin (Various)
Pamprin (Chattem)
Pepto Bismal (Proctor and Gamble)
Percodan (Dupont)
Percodan Demi (Dupont)
Propoxphene Compound 65 Capsules (CIU)(Teva)
Rite Aid Aspirin (Rite Aid)
Robaxisal (Robins)
Roxiprin (Roxane)
Salflex Tablets (Camrick)
Salsalate Tablets (Duramed)
Sine-Off (Hogil Pharmaceutical)
Soma Compound (Wallace)
Soma Compound W/Codeine (Wallace)
St. Joseph (Schering-Plough)
Synalgos DC (Wyeth Ayerst)
Talwin Compound (Sanofi-Winthrop)
Trilistate Liquid & Tablets (Purdue Frederick)
Vanquish (Sterling)
YSP (Carlsbad Technology)
Zorprin (Boots)

Because this is a partial list, ALWAYS check the ingredients in both prescription and over-the-counter medications for acetylsalicylic acid (ASA).