

***PROTOCOLS
FOR THE TREATMENT
OF
HEMOPHILIA
AND
VON WILLEBRAND DISEASE
(Revised March, 2009)***

Hemophilia of Georgia
8800 Roswell Road
Suite 170
Atlanta, Georgia 30350

**For 24-hour assistance in the management
of problems related to hemophilia call:**

Physician's Hemophilia
HOTLINE
1-800-PHYS-HOT
or 1-800-749-7468

Hemophilia of Georgia
9 a.m.-5 p.m. Weekdays
(770) 518-8272
1-800-866-HEMO
FAX: (770) 518-3310

NOTE: If you know the hemophilia treatment center with which the patient is affiliated, please contact that center directly. The names, addresses, and phone numbers of the treatment centers in Georgia can be found on pages 2 and 3 of these protocols.

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INTRODUCTION

Hemophilia of Georgia and the hemophilia treatment centers 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 center. It is hoped that communication between the patient's private physician and the hemophilia center 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 centers in the United States. Any treatment must be designed according to the needs of the individual and the resources available.

Hemophilia of Georgia would like to express our sincere appreciation to the Medical Advisory Committee for their input and expertise in preparing this revision of the *Protocols for the Treatment of Hemophilia and von Willebrand Disease*.

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PROTOCOLS FOR THE TREATMENT OF HEMOPHILIA AND VON WILLEBRAND DISEASE

I. HEMOPHILIA AND ITS DIAGNOSIS

Hemophilia A and B are X-linked disorders that are due to deficiencies of clotting factors VIII and IX respectively. The frequency of factor VIII deficiency is thought to be approximately 1 per 5,000-10,000 male births; for factor IX deficiency it is approximately 1 per 30,000-50,000 male births.

CLINICAL CLASSIFICATIONS OF PERSONS WITH EITHER HEMOPHILIA A OR HEMOPHILIA B

<u>Severe Hemophilia</u>	<u>Moderate Hemophilia</u>	<u>Mild Hemophilia</u>
<1% factor level	1-5% 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

****Normal factor levels are from 50-150%.***

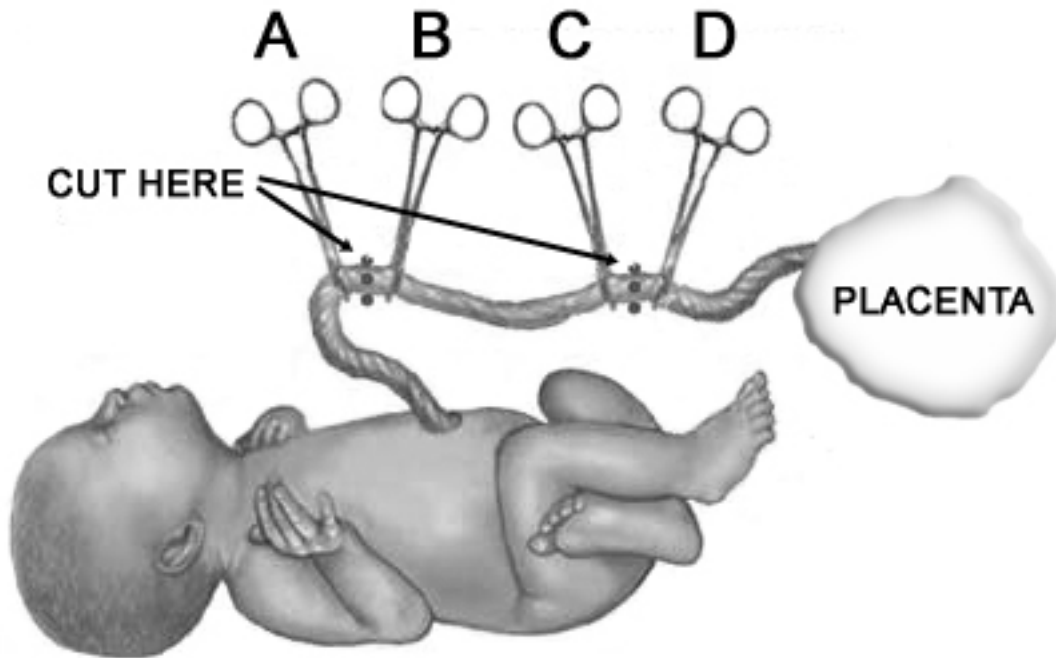
Early carrier detection is based on pedigree analysis, the measurement of the ratio of maternal factor VIII coagulant activity to von Willebrand factor and, more recently, DNA analysis. The maternal DNA-based diagnosis is the most accurate but is not informative in all patients. Prenatal diagnosis is 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 Hemophilia of Georgia or a hemophilia treatment center.

Postpartum diagnosis of hemophilia A relies on the ability to detect low factor VIII coagulant activity in a suspected newborn on cord blood (preferred) or a peripheral venous blood sample. The diagnosis of mild hemophilia B or factor IX deficiency is more difficult because the newborn normally has low levels of factor IX coagulant activity (a vitamin K dependent factor). Low levels of factor IX 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.



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Or 1-800-749-7468

**Suggested Technique for Collection of Cord Blood by Obstetricians
to Avoid Venipuncture of Newborn (for Factor VIII Assay)**



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

II. TREATMENT FOR BLEEDING EPISODES

For further recommendations, contact any of the hemophilia treatment centers in Georgia:

Emory University/Children's Healthcare of Atlanta - Comprehensive Hemophilia Program

- (1) Emory/CHOA-Egleston Campus (404) 727-1608
Emory University
Aflac Cancer Center and Blood Disorders Service
Outpatient Clinic
1405 Uppergate Drive NE 4th Floor
Atlanta, Georgia 30322
- (2) CHOA-Scottish Rite Campus (404) 785-3522
Aflac Cancer Center and Blood Disorders Service
5455 Meridian Mark Road – Suite 400
Atlanta, Georgia 30342

Physicians:

Thomas Abshire, M.D. (Adults and Pediatrics)
Maria Ribeiro, M.D. (Adults)
Sidney Stein, M.D. (Adults)

Christine Kempton, M.D. (Adults)
Amy Dunn, M.D. (Pediatrics)
Michael Briones, D.O. (Pediatrics)
Cassandra Josephson, M.D. (Pediatrics)
Shannon Meeks, MD (Pediatrics)
Carolyn Bennett, MD (Pediatrics)
Shawn Jobe, MD, Ph.D. (Pediatrics)

Backus Children's Hospital Center for Bleeding Disorders

Backus Children's Hospital at Memorial Health University Medical Center, Inc.
Department of Hematology/Oncology (912) 350-7285
4700 Waters Avenue
P.O. Box 23089
Savannah, Georgia 31403-3089

Physician: Cynthia E. Gonzales, M.D. (Pediatrics)

Medical College of Georgia Comprehensive Hemophilia Program

Medical College of Georgia (706) 721-0870
Department of Adult Hematology/Oncology
1521 Pope Avenue
Augusta, Georgia 30912

Physician: Kavita Natarajan, M.B.B.S.

Medical College of Georgia (706) 721-3626
Department of Pediatric Hematology/Oncology
1446 Harper Street BG-2011
Augusta, Georgia 30912-3730

Physician: Afshin Ameri, M.D.

Hemophilia of Georgia is involved in the coordination and support of these centers. For further information, call (770) 518-8272.

A. Basic Principles of Treatment

1. Treat bleeds early with factor replacement therapy, i.e., within 2 hours of the onset of symptoms. Do not wait for appearance of physical signs.
 - (a) Treat a suspected intracranial hemorrhage immediately.



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- (b) Most patients, even young children, can recognize joint hemorrhage early in its course. Early recognition and treatment will limit soft tissue damage. In addition, less factor is ultimately needed.
 - (c) **IF IN DOUBT, TREAT.** If a hemophiliac has sustained an injury or if he thinks he may be bleeding, treat first and perform diagnostic tests later.
2. Treat veins with care. A hemophiliac's veins are his lifeline.
 - (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 aspirin. (See Appendix, page 21.) 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.
 4. Home therapy with clotting factor is usually begun when a child is one 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 center is a state-of-the-art approach to hemophilia treatment. In this setting, the patient is evaluated by a multi-disciplinary team that usually consists of a hematologist, orthopedist, nurse coordinator, social worker and physical therapist and may also consist of a dietician, infectious disease specialist, hepatologist, dentist, occupational therapist, vocational rehabilitationist, psychologist and genetic counselor. 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 center is essential for optimal management.

B. Options Available for the Treatment of a Person with Factor VIII Deficiency (Hemophilia A)

1. Factor VIII

Commercially prepared, lyophilized factor VIII 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: (1) recombinant products, which include Kogenate FS, Helixate FS, Advate, Recombinate and Xyntha; (2) monoclonal antibody purified products, which include Hemofil M and Monoclate P; and (3) intermediate and "high-purity" factor VIII products, which include Koate-DVI, Humate P and Alphanate (all of which have been used to treat von Willebrand Disease, although only Humate P and Alphanate are currently licensed for such use). Consult the product insert guide for specific

instructions. All of these products have undergone viral attenuation. Hemophilia of Georgia does not endorse one particular brand.

There may be specific product recommendations for patients with complications such as inhibitors or HIV infection. NovoSeven (recombinant activated factor VIIa) is licensed for the treatment of bleeding in patients with inhibitors to factor VIII or factor IX. The standard dose is 90 mcg/kg given every 2-3 hours until hemostasis is achieved or until treatment is thought to be ineffective. FEIBA (Factor VIII Inhibitor Bypassing Agent) is also utilized for bleeding in patients with inhibitors. The standard dose is 75-100 units/kg given every 12-24 hours. Consult a hemophilia treatment center at the initiation of therapy if the patient has a problem more complicated than a simple bleed.

- (a) These products are available for home therapy through Hemophilia of Georgia. Products are shipped directly to the home. Financial assistance for Georgia residents is available for the acquisition of these products and is based upon the individual patient's need.
- (b) Vials are available in dosages ranging between approximately 250-3000 units each.
- (c) Each factor VIII unit per kilogram of body weight infused intravenously will raise the plasma factor VIII level approximately 2%. The half-life is approximately 8-12 hours.
- (d) The formula for calculating the dosage for factor VIII 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 factor VIII

Refer to the chart on page 20 for suggested factor level and dosage based on type of hemorrhage.

- (e) Factor VIII 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.
- (f) Always give the entire content of each vial of factor VIII even if that exceeds the calculated dosage. Factor is expensive and should not be wasted.
- (g) In patients where factor VIII inhibitor status is unknown or is in question, determination of factor recovery in 1 to 2 hours after infusion by measuring factor VIII levels may be advisable.
- (h) Continuous infusion of factor VIII should be supervised by an experienced hematologist. A 50 unit/kg bolus followed by 4–5 units/kg per hour of factor VIII will provide a factor VIII level of approximately 100% in a patient with severe hemophilia A. Daily factor levels must be monitored.



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Factor VIII products are stable in IV solutions for at least 12 hours at room temperature. Therefore, 12-hour bags of factor for continuous infusion may be prepared by the pharmacy under a hood and administered without concern for proteolytic inactivation, degradation, or bacterial contamination.

2. **Cryoprecipitate**

Because Cryoprecipitate has not undergone viral attenuation, it should be used to treat bleeding in patients with hemophilia A only if factor VIII is not available. The average factor VIII content per bag of Cryo is 60-100 units.

3. **DDAVP**

DDAVP, a synthetic vasopressin analogue and the intra-nasal formulation of DDAVP (Stimate™) are useful in the treatment of persons with mild hemophilia who have a 5% or greater factor VIII level and who have been shown through pre-testing to be responsive to its infusion.

DDAVP releases stored factor VIII into the circulation and increases the factor VIII 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. Repetitive use will lead to diminished response. Prior to therapeutic use, DDAVP should be evaluated as follows: measure the factor level pre-infusion; infuse DDAVP (0.3 micrograms per kilogram of body weight diluted in 30-50 cc of normal saline) slowly, over a 15-30 minute period; measure the factor VIII level 30-60 minutes post-infusion.

Stimate™, an intra-nasal preparation of DDAVP, is fifteen times more concentrated than the standard intra-nasal DDAVP used for treating diabetes insipidus and enuresis. RX: one spray in a single nostril for children old enough to sniff on command and under 50 kg and one spray in each nostril for patients weighing over 50 kg. Because of marked variability in response to intra-nasal 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 of isotonic fluids is important and the serum sodium must be monitored during periods of repetitive daily use of DDAVP or Stimate™. Patients can generally drink Gatorade®(G or G2) without fluid restriction. 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 will exceed a single dose should be discussed with a physician familiar with the use and complications of this medication.

4. **Antifibrinolytic Agents**

- (a) Epsilon-aminocaproic acid (Amicar or 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 milligrams/kg (max 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 (Cyklokapron, TECA, or TA) is another antifibrinolytic agent but the oral form is not readily available in the U.S. A dose of 25 milligrams/kg orally every eight hours for ten 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 Amicar (EACA).

C. **Options Available for the Treatment of a Person with Factor IX Deficiency (Hemophilia B)**

1. **Factor IX**

Commercially prepared, heat-treated, lyophilized factor IX products from plasma are distributed under a variety of brand names. Since 1991, new products have been introduced which have undergone viral attenuation. These plasma products fall into two classes: (1) pure coagulation factor IX products, which include AlphaNine SD and Mononine; and (2) factor IX complex concentrations which are currently unavailable. Also available is a recombinant factor IX product, Benefix. 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 center for these recommendations.

The pure coagulation factor IX products (including AlphaNine SD and Mononine) are thought to be largely free of the risks of thrombosis and DIC-related complications.

- (a) These products are available for home therapy use through the Hemophilia of Georgia Pharmacy. Products are shipped directly to the home. Financial assistance for Georgia residents is available for acquiring these products and is based upon the individual patient's need.
- (b) Vials are available in dosages ranging between approximately 250-1000 units each.
- (c) Each factor IX unit per kilogram of body weight infused intravenously will raise the plasma factor IX 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 IX level by 1%.



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- (d) The formula for calculating the dosage for plasma factor IX 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 factor IX

Refer to the chart on page 20 for suggested factor level and dosage based on type of hemorrhage.

- (e) Factor IX should be infused by slow IV push at a rate not to exceed a volume of 3 ml per minute.
- (f) In patients where factor IX inhibitor status is unknown or in question determination of factor recovery in 1 to 2 hours after infusion by measuring factor IX levels may be advisable.
- (g) Continuous infusion of purified factor IX should be supervised by an experienced hematologist.

2. **Fresh Frozen Plasma (FFP)**

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

3. **Antifibrinolytic Agents**

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

D. **Specific Hemorrhages**

1. **Joint Hemorrhage**

- (a) First give the patient the appropriate dose of factor 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 one of the hemophilia treatment centers.
- (c) A second infusion to raise the factor level to 40-50% in 24 hours (hemophilia A) or in 48 hours (hemophilia B) and a third infusion to 40-50% (Hemophilia A) in 72 hours is recommended in children and may be needed in adults if symptoms persist (i.e., if swelling and/or pain is not significantly improved).

- (d) The so-called “target joint bleeding” protocol where the patient receives 80-100% correction on the day of the bleed (day 1), and 40-50% correction on day 2 and 4 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 applied to area of bleeding, temporary rest, and elevation.
- (g) Seek consultation at a hemophilia treatment center if symptoms persist beyond three days or if a fracture is suspected.
- (h) Pain control: aspirin-free medication. (See Appendix, page 21.)

2. **Muscle Hemorrhage**

- (a) First give the patient the appropriate dose of factor and then evaluate.
- (b) Raise the factor level to 40-50% 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 5 or 8 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.

3. **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., CT scan or ultrasound, will confirm the diagnosis of an iliopsoas hemorrhage and help differentiate from acute appendicitis, for which this condition is often mistaken.



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

4. **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 center 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 MRI should be performed.
- (d) In the case of a CNS bleed, refer to a hemophilia treatment center.
- (e) In the case of suspected head trauma, first treat the patient with factor and then evaluate.
- (f) Severe headache may be a manifestation of HIV-related opportunistic infection. (See section IV, C, HIV Issues, page 17.)

5. **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 center 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.

6. **Acute Gastrointestinal Hemorrhage**

- (a) First give the patient the appropriate dose of factor 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) Amicar (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 center for recommendations.

7. **Acute Abdomen Hemorrhage**

- (a) Acute abdomen hemorrhage can mimic a number of infectious conditions and appropriate radiological studies are often necessary. Iliopsoas hemorrhage should be ruled out. (See section II, D, 3, Iliopsoas Hemorrhage, sections (a) and (b), page 9.)
- (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 center for recommendations.

8. **Ophthalmic Trauma or Hemorrhage**

- (a) First give the patient the appropriate dose of factor and then evaluate.
- (b) Immediately raise the factor level to 80-100%. 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 or hemorrhage to help prevent vision loss.

9. **Renal Hemorrhage**

- (a) Avoid use of antifibrinolytic agents for renal bleeding unless directed by a hemophilia treatment specialist. Lower urinary tract bleeding may respond to antifibrinolytic therapy.
- (b) Painless hematuria should be treated with bedrest and vigorous hydration (1-1/2 times maintenance) for 48 hours.



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- (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 milligram/kg x 3 days) could be used though benefit is unclear.

10. **Oral Hemorrhage**

- (a) Bleeding may be controlled with the use of Amicar (EACA) or tranexamic acid alone, or with the use of factor and either Amicar (EACA) or tranexamic acid, if bleeding is prolonged, significant, or difficult to control. Treatment of a frenulum bleed in infants should be treated aggressively 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, but red ones should be avoided to evaluate for further bleeding. A soft, cold diet for 24 hours is recommended.
- (d) Consult a hematologist, a dentist or an otolaryngologist as indicated.
- (e) A custom fit mouthpiece might be helpful to provide local compression.

11. **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 10-20 minutes without turning loose.
- (c) For bleeds related especially to allergies, URI or seasonal changes, try Neo-Syneprine® .5%-1%, two drops each nostril b.i.d. X 3 days. The use of a cold mist vaporizer may also be helpful.
- (d) Watch for anemia if bleeding is prolonged or occurs frequently.
- (e) ENT consultation may be indicated.
- (f) The use of EACA (Amicar) or tranexamic acid may be helpful.
- (g) Use of normal saline solution or gel (Ayr™/Little Noses®) is extremely useful.
- (h) Nose clips might be helpful to keep pressure applied for 10-20 minutes.

12. 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.

13. 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.

E. 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 thus is as likely to affect females as commonly as males. The disease is due to a reduction or abnormality of a glycoprotein (called von Willebrand factor or 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 factor VIII, factor VIII activity in the blood is sometimes decreased in proportion to the reduction in measurable von Willebrand factor.

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 or 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 factor VIII—these patients may behave like those with moderate hemophilia. This type of von Willebrand Disease should be diagnosed and treated only by a hematologist who specializes in VWD and hemophilia.



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Symptomatic individuals with VWD will usually present with mucosal bleeding (e.g., epistaxis, heavy menses, oral, GI or 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 well consultation with gynecology. DDAVP and antifibrinolytic agents may also help. Rarely, people with severe or type 3 VWD experience the joint and muscle bleeding frequently observed in people with hemophilia. They can also have surgical bleeding which is usually immediate and if corrected, does not manifest the delayed bleeding seen in hemophiliacs. It is recommended to coordinate all surgery with the hemophilia treatment center.

The mainstays of treatment for VWD are DDAVP and Factor VIII rich in VWF. Bleeding patients with Type 1 VWD can generally be treated with DDAVP (see page 6); some patients with Type 2A may also respond to its use. If DDAVP is either not available, or its use gives an inadequate clinical response or is poorly tolerated by the patient, any VWF rich concentrate (see below) can be used to treat patients with Types 1 and 2A. 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 factor VIII rich in VWF. The concentrate currently available with the highest concentration of VWF is called Humate-P. Other factor VIII products that contain substantial amounts of VWF are Alphanate SD and Koate DVI. All of these 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 4. Highly purified factor VIII—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 virally attenuated, its use is not recommended unless a concentrate is not available.

III. OTHER MANAGEMENT ISSUES

A. Dental

1. Routine examinations and cleaning generally can be performed without raising the factor level. Adequate coverage (i.e., factor 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 local anesthesia via a nerve block is given. 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 that raises the level to 50-100%. Antifibrinolytic products should be used concomitantly with factors or DDAVP. The dose for Amicar (EACA), started prior to the procedure, is 50-100 milligrams/kg every six hours, for

seven to ten days (maximum 24 grams per 24 hours). The dose for tranexamic acid is 25 milligrams/kg orally every eight hours for seven to ten days. Unless contraindicated, we generally recommend the use of antifibrinolytic agents until the sutures dissolve.

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, Amicar can be used. 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; for example, procedures requiring sutures, multiple extractions, etc.
6. The position of the third molars (wisdom teeth) should be evaluated during 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 for several days after wisdom teeth extractions in addition to antifibrinolytic therapy with Amicar.
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 center hematologist.

B. Surgery

1. Management of the surgical patient is best undertaken at a hemophilia treatment center. 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, the presence of an inhibitor should be considered. See section IV, A, Factor Inhibitor, page 16.) Immediately prior to the procedure, raise the calculated factor level to 80-100%; maintain at least a 50% level for one to two weeks, depending on the type of surgery.



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Continuous infusion factor may be preferable for the management of surgical patients when factor with stability data for continuous infusion is 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.

C. Invasive Procedures

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

D. 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 5 minutes.
2. Immunocompromised patients should not receive live viral vaccines where the risk of infection outweighs complications of the vaccine. Do not give oral polio.
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. Vaccine 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 hemophiliacs. Antibody to hepatitis B virus should be determined following the full immunization schedule to ensure immunity.

E. 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.

IV. COMPLICATIONS OF HEMOPHILIA

A. 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.

B. Synovitis

1. The clinical findings are a distended (but not tense or painful) joint, usually the knee, ankle or elbow.
2. Synovitis may mimic an acute bleed. If hemorrhage is ruled out, treatment with a non-steroidal, anti-inflammatory may be used, but the patient should be warned about the potential for increased bleeding. Cox-2 inhibitor non-steroidals such as Celebrex may have less potential for causing bleeding. Chronic use of Celebrex should be limited to 200 milligrams per day and be done with caution in older patients and those with risk factors for cardiovascular disease. Do not use aspirin-containing medications. Refer the patient for multidisciplinary evaluation at a hemophilia treatment center.
3. This problem is difficult to manage and is best handled by a team approach, specifically by the hematologist, orthopedist and physical therapist at the hemophilia treatment center.

C. HIV Issues

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, health care providers should be aware of the probability of HIV infection in a person with hemophilia born before 1985. A significant percent of HIV-infected hemophiliacs 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 (shingles)
 - pneumonia
 - chronic diarrhea
 - lymphadenopathy



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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 factors available since 1985 and the new recombinant products have eliminated the risk of HIV infection. **Therefore, patients born after 1985 are 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 counseling are available through our comprehensive hemophilia centers and/or Hemophilia of Georgia. HIV risk reduction counseling is also available.
6. If a health care worker sustains a significant exposure to blood or body fluids from a patient with hemophilia, the potential for transmission of bloodborne pathogens should be considered. In addition to having HIV infection, many persons with hemophilia also have chronic hepatitis C infection and a few have chronic hepatitis B.

D. Hepatitis C

1. Most persons with hemophilia who received clotting factor before 1990 acquired hepatitis C infection. Almost all hemophiliacs with HIV infection have hepatitis C co-infection. Hepatitis C infection causes chronic hepatitis in >80% of cases and can lead to cirrhosis and liver cancer.
2. Although hepatitis C is more readily transmitted by blood exposure than HIV, sexual transmission of hepatitis C is uncommon in heterosexual couples.
3. Alcohol consumption can accelerate the progression of hepatitis C liver injury and its use should be discouraged.
4. Persons with chronic hepatitis C are more susceptible to the hepatotoxic effects of other drugs. Acetaminophen is not contraindicated in chronic hepatitis C, although those with cirrhosis should use with caution.
5. Persons with chronic hepatitis C can have a more severe illness should they contract hepatitis A or B; consequently, persons with hepatitis C infection should be screened for hepatitis A and B and offered vaccine should they be non-immune.

6. Although treatment of hepatitis C 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 center with expertise in managing clotting factor infusion.

E. 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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DESIRED PLASMA FACTOR LEVEL AND DOSAGE FOR BOLUS INFUSIONS

<u>TYPE OF HEMORRHAGE</u>	<u>HEMOPHILIA A (VIII)</u>		<u>HEMOPHILIA B (IX)</u>	
	<u>Desired Level</u>	<u>Dose (units/kg)</u>	<u>Desired Level</u>	<u>Dose* (units/kg)</u>
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 Factor IX, 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.

NOTE: In patients where factor inhibitor status is unknown or is in question, determination of factor recovery in 1 to 2 hours after infusion by measuring factor levels may be advisable.

APPENDIX

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)
Lortab ASA (Whitby)
Magan Tablets (Savage)
Magnaprin (Rugby)
Magsal Tablets (U.S. Pharmaceutical)
Methocarbamol & Aspirin Tablets (PAR)

Methocarbamol w/ASA (Various)
Midol (Bayer)
Mono-Gesic Tablets (Schwarz)
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 (A.S.A.).