PROTOCOLS
FOR THE TREATMENT
OF
HEMOPHILIA
AND
VON WILLEBRAND DISEASE
(Revised February, 2015)

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.

Hemophilia of Georgia
8800 Roswell Road
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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.

CLASSIFICATION OF PERSONS WITH EITHER HEMOPHILIA A OR HEMOPHILIA B

<table>
<thead>
<tr>
<th>Severe Hemophilia</th>
<th>Moderate Hemophilia</th>
<th>Mild Hemophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1% factor level</td>
<td>1-5% factor level</td>
<td>6-40 % factor level</td>
</tr>
</tbody>
</table>

CLINICAL FEATURES OF PERSONS WITH EITHER HEMOPHILIA A OR HEMOPHILIA B

<table>
<thead>
<tr>
<th>Severe Hemophilia</th>
<th>Moderate Hemophilia</th>
<th>Mild Hemophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>spontaneous bleeding characteristic</td>
<td>can bleed with slight injury</td>
<td>bleeding typically only with severe injury, surgery, invasive procedures</td>
</tr>
<tr>
<td>may bleed 1 to 2 times per week</td>
<td>may bleed 1 time per month</td>
<td>may never have a bleeding problem</td>
</tr>
<tr>
<td>characterized by joint bleeding (hemarthrosis)</td>
<td>may have joint bleeding</td>
<td>rarely has joint bleeding</td>
</tr>
</tbody>
</table>

*Normal factor levels are from 50-150%.

Early carrier detection is based on pedigree analysis and DNA analysis. The maternal DNA-based diagnosis is the most accurate but is not informative in all patients. Since factor VIII and IX levels can vary in carriers of hemophilia, factor levels cannot be used to determine carrier status, though they are useful to determine the carrier’s own risk of bleeding.

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.

**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:

Comprehensive Bleeding Disorders Center at Emory University and Children’s Healthcare of Atlanta

(1) Emory/CHOA-Egleston Campus
Emory University
Aflac Cancer and Blood Disorders Center
1405 Uppergate Drive NE 4th Floor
Atlanta, Georgia 30322

(404) 727-1608
Physicians:

Christine Kempton, M.D., MSc (Director)
Maria Ribeiro, M.D. (Adults)
Sidney Stein, M.D. (Adults)
Ana Antun, M.D. (Adults)
Duc "Bobby" Tran, MD (Adults)
Michael Briones, D.O. (Pediatrics)
Shannon Meeks, M.D. (Pediatrics)
Carolyn Bennett, M.D., MSc (Pediatrics)
Robert Sidonio, M.D., MSc (Pediatrics)

The Children's Hospital at Memorial Health University Medical Center, Inc.

The Children's Hospital at Memorial Health University Medical Center, Inc.
Department of Hematology/Oncology (912) 350-8194
4700 Waters Avenue
P.O. Box 23089
Savannah, Georgia 31403-3089

Physician: Martin Johnston, MD

Georgia Regents University Comprehensive Hemophilia Program

Georgia Regents University (706) 721-0870
Department of Adult Hematology/Oncology
1120 15th Street, BAA5407
Augusta, Georgia 30912-3125

Physician:

Georgia Regents University (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.
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.

**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 once treatment is completed.

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 22.) Non-steroidal, anti-inflammatory agents should be used with caution. We recommend acetaminophen with or without codeine for pain control.

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, nurse coordinator, social worker and physical therapist and may also consist of an orthopedist, dietician, infectious disease specialist, hepatologist, dentist, occupational therapist, vocational rehabilitationist, psychologist and genetic counselor. This team devises a coordinated care plan for the patient. A local physician may participate by providing close follow-up in between visits to the hemophilia treatment center.

Communication between the patient’s local 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, Xynta and Alprolix; (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, Wilate and Alphanate (all of which have been used to treat von Willebrand Disease, although only Humate P, Wilate and Alphanate are currently licensed for such use). Wilate
is not approved for treatment of hemophilia. 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 50-100 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. Social workers are available to help Georgia residents explore insurance options.

(b) Vials are available in dosages ranging between approximately 250-3000 units each.

(c) For patients without a factor VIII inhibitor, 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. The presence of a factor VIII inhibitor may decrease both recovery and half-life.

The formula for calculating the dosage for factor VIII is taking the patient’s weight in kilograms, multiplying by the factor level desired, and then dividing by the recovery level (typically 2 IU/dl per IU/kg), which will indicate the number of factor units required.

Formula: \[
\text{Target Factor Level (IU/dl) – Baseline Factor Level (IU/dl)} \times \text{wt in Kg} \div \text{Factor Recovery (IU/dl per IU/kg)}
\]

- The target minus the baseline is equal to the desired change in factor level

Example: For a 45 kg boy with severe hemophilia A who has a joint bleed for which the desired factor level is 40%, the following equation is used:

\[
40 \times 45 \text{ kg} \div 2 = 900 \text{ units of factor VIII}
\]

Refer to the chart on page 21 for suggested factor level and dosage based on type of hemorrhage.

(d) Factor VIII should be infused by slow IV push. Consult the product insert guide for specific instructions.

(e) Do not waste the content of a prescribed vial. 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.
(f) In patients where factor VIII inhibitor status is unknown or is in question, determination of factor recovery in 15-30 minutes after completion of the infusion by measuring factor VIII levels may be advisable.

(g) In the setting of a limb or life-threatening bleed or major surgery, continuous infusion of factor VIII could be considered when supervised by an experienced hematologist. A 50 IU/kg bolus followed by 4–5 IU/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.

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 in patients with mild hemophilia A. This increased factor VIII level 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 daily 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, repetitive use leads to a diminished response. Accordingly, Stimate™ use should be limited to once every 24 hours over a maximum period of three days.

Fluid restriction to 3/4 maintenance of isotonic fluids is important. When intravenous fluids are being administered in the setting of repetitive daily use of DDAVP or Stimate™, the serum sodium should be monitored.
Patients can generally drink Gatorade®(G or G2) without fluid restriction. Additionally, patients should contact their healthcare providers if they have symptoms of severe headache, weakness, or vomiting. The risk of hyponatremia is greatest in children.

4. **Antifibrinolytic Agents**

(a) Epsilon-aminocaproic acid (Amicar or EACA) is an antifibrinolytic agent that can be used along with factor VIII products, particularly 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 five to ten days (maximum 24 grams per 24 hours). A liquid preparation is available and a mouthwash can be prepared for topical administration.

(b) Tranexamic acid (Cyklokapron™, TECA, or TA) is another antifibrinolytic agent. The oral form (Lysteda™) is approved for use in adults with heavy menstrual bleeding. It is expected that this agent will also be effective in the treatment of other mucosal bleeds given its mechanisms of action. Lysteda™ is available in 650 mg tablets. Lysteda™ administration of 1300 mg three times a day for five days is recommended for the treatment of menorrhagia.

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

1. **Factor IX**

As with factor VIII, there are both plasma-derived and recombinant factor IX products available. Recombinant factor IX products include BeneFIX, Rixubis, and Alprolix. Consult the product insert guide for specific instructions. Hemophilia of Georgia does not endorse a particular brand.

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. Social workers are available to help Georgia residents explore insurance options.

(b) Vials are available in varying dosages.

(c) Each plasma derived factor IX IU 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 IU/kg in adults and 1.5 units/kg in children will raise the IX level by approximately 1%.

(d) The formula for calculating the dosage for plasma factor IX concentrate is taking the patient’s weight in kilograms and multiplying by the factor level desired, which will indicate the number of factor units required.
Formula: \[
\frac{[\text{Target Factor Level (IU/dl)} - \text{Baseline Factor Level (IU/dl)}]}{\text{Factor Recovery (IU/dl per IU/kg)}} \times \text{wt in Kg}
\]
- The target minus the baseline is equal to the desired change in factor level

Example: For a 45 kg boy with severe hemophilia B who has a joint bleed for which a factor IX level of 40% is desired, use the following equation:

\[40 \times 45 \text{ kg} + 1 = 1800 \text{ units of factor IX.}\]

If BeneFIX is used, multiply by 1.5 (children) or 1.2 (adults).

Refer to the chart on page 21 for suggested factor level and dosage based on type of hemorrhage.

(e) Factor IX should be infused according to the prescribing information. Recombinant products typically can be infused over several minutes whereas plasma-derived products may require slower infusion rates.

(f) In patients where factor IX inhibitor status is unknown or in question, determination of factor recovery in 15-30 minutes 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 product 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 are indicated in the setting of trauma where injury to the bone is suspected.

(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 (defined as three bleeds into a single joint during the previous 6 months) 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 are 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 in which 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 22.)

2. **Muscle Hemorrhage**

(a) First give the patient the appropriate dose of factor and then evaluate. Look particularly for signs of neurovascular compromise (i.e., compartment syndrome).

(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. Continue to monitor 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. This is considered a serious bleed as significant “occult” blood loss may occur leading to anemia, possible compartment syndrome and femoral nerve damage.

(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.
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 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 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 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.

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 aggressive 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) Especially for bleeds related to allergies, URI or seasonal changes, try Neo-Synephrine® .5%-1%, two drops each nostril b.i.d. X 3 days. Even in the absence of allergies or URI, this may be effective because of vaso-constriction. 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 for prevention of epistaxis.

(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 retropharyngeal, mediastinal, or 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 inherited on an autosomal basis and thus affects females and males equally. 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 most commonly measured as ristocetin cofactor activity. There are several variants of Type 2; the most important to distinguish is Type 2B because of possible 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.

Symptomatic individuals with VWD will usually present with mucosal bleeding (e.g., epistaxis, oral, GI or GU bleeding, or easy bruising). Heavy menstrual bleeding is a common problem for women with this bleeding disorder.

The mainstays of treatment for VWD are DDAVP and factor VIII concentrates 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.
DDAVP may be given intranasally or intravenously and causes release of VWF from storage sites. It is effective for 2-3 days before tachyphylaxis occurs. Patients should be tested to ensure a response before it is prescribed for treatment of bleeding symptoms.

It is important to note that there is a risk of hyponatremia with DDAVP administration and fluid intake should be carefully monitored. If DDAVP is not available, gives an inadequate clinical response or there is severe or life-threatening bleeding, the treatment of choice is any VWF rich concentrate (see below). Those with Types 2B, 2N, 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 most widely available is called Humate-P. Other factor VIII products that contain substantial amounts of VWF are Alphanate SD, Wilate 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. All of these products with the exception of Koate DVI are licensed for the treatment of VWD and the lyophilized bottles containing these products are labeled in both ristocetin cofactor units and factor VIII units. 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.

For mucosal bleeding, treatment with anti-fibrinolytics, aminocaproic acid or tranexamic acid can also help. For women with heavy menstrual bleeding, hormonal therapy with various forms of estrogen replacement may help, as well as DDAVP and antifibrinolytic agents, such as Lysteda™.

Given the risk of bleeding in all VWD patients with surgery, a bleeding treatment plan should be established with the help of a hematologist specializing in bleeding disorders prior to the procedure taking place. All patients should wear a medic alert and have an emergency treatment letter 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 up to seven to ten days (maximum 24 grams per 24 hours). The dose for tranexamic acid is 25 milligrams/kg orally every eight hours for up to seven to ten days. Unless contraindicated, we generally recommend the use of antifibrinolytic agents until the sutures dissolve and the site is well healed. Factor infusions after the extractions may also be necessary.

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 or tranexamic acid.

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 17.)
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. Continuous infusion of factor may be preferable for the management of surgical patients. 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. Many vaccinations can be given subcutaneously, which is the preferred route for immunizing persons with hemophilia. A few vaccinations are to be given intramuscularly only and the effectiveness of giving these vaccinations subcutaneously is unknown. There is good evidence for the effectiveness of both hepatitis A and B vaccinations given subcutaneously in persons with hemophilia. For other vaccinations, refer to the prescribing information for the appropriateness of subcutaneous administration. If a vaccination is to be given intramuscularly, some patients may need to receive factor replacement prior to the injection. The smallest size needle (23 gauge or smaller) should be used and firm pressure without rubbing should be applied for 5 minutes after the injection. Subcutaneous injections can be given without factor replacement therapy even in patients with severe hemophilia.

2. Live viral vaccines should not be given to immunocompromised patients without consultation with an ID specialist.

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. Following treatment of any suspected bleeding, treatment is directed at decreasing inflammation. Cox-2 inhibitor non-steroidals such as Celebrex have less potential bleeding as they do not inhibit platelet function and could be considered in this setting. Use of Celebrex should be limited to the lowest effective dose. Caution should be used when Celebrex is used in the setting of hepatic impairment. Doses should be reduced by 50% in patients with Child-Pugh class B hepatic impairment and use is not recommended in the setting of severe hepatic dysfunction. 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 bloodborne 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 persons with acute or advanced HIV infection 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

2. Causes of pneumonia in this setting include *Pneumocystis jiroveci* (PJP), formerly known as *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 bleeding 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. 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 hepatocellular carcinoma (liver cancer).

2. Hepatitis C is primarily spread through blood/percutaneous transmission. 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 and should limit acetaminophen dosage to <2 gm/day.

5. Nonalcoholic fatty liver disease (NAFLD) is also a risk factor for fibrosis progression in patients with hepatitis C. Patients who are overweight or obese should be counseled on diet, exercise and medical therapies to reduce weight and improve insulin resistance.
6. 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.

7. Liver biopsy still remains the gold standard for staging severity of hepatitis C infection and fibrosis, though newer modalities are emerging.

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.

8. Although treatment for hepatitis C has many side effects, newer treatment regimens using combinations of directly acting antiviral agents (DAAs) have emerged with improved side effect profiles and efficacy. Treatment should be coordinated with a hepatitis C specialist. Current recommended regimen for treatment – naïve patients:
   - Genotype 1: daily sofosbuvir (400 mg) and weight-based ribavirin plus weekly pegylated interferon x 12 weeks OR daily sofosbuvir (400mg) plus simeprevir (150mg) with or without weight-based ribavirin in those ineligible to receive IFN.
   - Genotype 2: daily sofosbuvir (400mg) and weight-based ribavirin x 12 weeks
   - Genotype 3: daily sofosbuvir (400mg) and weight-based ribavirin x 24 weeks
   - Genotype 4: daily sofosbuvir (400mg) and weight-based ribavirin plus weekly pegylated interferon x 12 weeks OR daily sofosbuvir (400mg) plus simeprevir (150mg) x 24 weeks in those ineligible to receive IFN.

Treatment with pegylated interferon and ribavirin with or without telaprevir or boceprevir is no longer recommended for genotype 1 patients due to increased rates of adverse reactions/drug interactions, longer treatment times and complex dosing regimens. Additionally, treatment with pegylated interferon and ribavirin alone is no longer recommended for genotypes 1-4 due to inferior efficacy to regimens containing directly acting antiviral agents.

Given improved efficacy of the new DAAs, patients who failed prior HCV treatment should be considered for re-treatment. Regimens and efficacy vary based on HCV genotype as well as prior response to therapy (relapse, partial responder or null responder). Refer to published AASLD/IDSA guidelines for further information.

Hepatitis C patients with cirrhosis should be screened for liver cancer and esophageal varices according to published guidelines. The determination of the presence of cirrhosis should be made using a combination of clinical judgment, imaging and liver biopsy.

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. It is important to realize that anaphylaxis can be associated with inhibitor development in patients with hemophilia B.

4. Sometimes, changing factor brand may reduce symptoms.
## DESIRED PLASMA FACTOR LEVEL AND DOSAGE FOR BOLUS INFUSIONS

<table>
<thead>
<tr>
<th>TYPE OF HEMORRHAGE</th>
<th>HEMOPHILIA A (VIII)</th>
<th>HEMOPHILIA B (IX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Desired Level (IU/kg)</td>
<td>Desired Level (IU/kg)</td>
</tr>
<tr>
<td>Joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>40-50%</td>
<td>40-50%</td>
</tr>
<tr>
<td>Children</td>
<td>80-100%</td>
<td>80-100%</td>
</tr>
<tr>
<td>Muscle (except Iliopsoas)</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Iliopsoas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>80-100%</td>
<td>80-100%</td>
</tr>
<tr>
<td>Maintenance</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>CNS/Head</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>80-100%</td>
<td>80-100%</td>
</tr>
<tr>
<td>Maintenance</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Throat and Neck</td>
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<td></td>
</tr>
<tr>
<td>Initial</td>
<td>80-100%</td>
<td>80-100%</td>
</tr>
<tr>
<td>Maintenance</td>
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<td>50%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
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<td>Initial</td>
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<td>80-100%</td>
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<tr>
<td>Maintenance</td>
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<td>50%</td>
</tr>
<tr>
<td>Ophthalmic</td>
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<tr>
<td>Maintenance</td>
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<tr>
<td>Renal</td>
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<tr>
<td>Deep Laceration</td>
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<td>50-100%</td>
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<td>Surgery</td>
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</tr>
<tr>
<td>Initial</td>
<td>80-100%</td>
<td>80-100%</td>
</tr>
<tr>
<td>Maintenance</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

* For recombinant Factor IX, multiply x 1.2 – 1.5. In general, the younger the child the higher the correction factor with 1.2 appropriate for most.

** 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 15-30 minutes after infusion by measuring factor levels may be advisable.

For severe bleeds that are limb – or life-threatening, the trough level should be kept above 50%.
<table>
<thead>
<tr>
<th>Common Preparations Containing Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acuprin 81</td>
</tr>
<tr>
<td>Aggrenox Capsules</td>
</tr>
<tr>
<td>Alka Seltzer (all preparations)</td>
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<tr>
<td>Alka Seltzer w/Aspirin</td>
</tr>
<tr>
<td>Alor</td>
</tr>
<tr>
<td>Anacin</td>
</tr>
<tr>
<td>Arthritis Pain Formula</td>
</tr>
<tr>
<td>Ascripton</td>
</tr>
<tr>
<td>Aspergum</td>
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<tr>
<td>Aspidrox</td>
</tr>
<tr>
<td>Aspircaf</td>
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<tr>
<td>Aspir-Mox</td>
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<tr>
<td>Aspirtab</td>
</tr>
<tr>
<td>Aspir-trin</td>
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<tr>
<td>Axotal Tablets</td>
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<tr>
<td>Azdone</td>
</tr>
<tr>
<td>Bayer</td>
</tr>
<tr>
<td>Bayer Childrens</td>
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<tr>
<td>B-C Cold-Sinus-Allergy Powder</td>
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<tr>
<td>B-C Powder</td>
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<tr>
<td>B-C Tablets</td>
</tr>
<tr>
<td>Bufferin</td>
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<tr>
<td>Buffex</td>
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<tr>
<td>Carisoprodol Compound</td>
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<tr>
<td>Cosprin Tablets</td>
</tr>
<tr>
<td>CVS Aspirin</td>
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<tr>
<td>Darvon Compound-65</td>
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<tr>
<td>Damason-P</td>
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<td>DeWitt's Pills</td>
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<tr>
<td>Disalcid Capsules and Tablets</td>
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<tr>
<td>Doans</td>
</tr>
<tr>
<td>Dristan</td>
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<tr>
<td>Easprin</td>
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<tr>
<td>Ecotrin</td>
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<tr>
<td>Empirin</td>
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<td>Endodan Tablets</td>
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<tr>
<td>Entaprin</td>
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<tr>
<td>Entercote</td>
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<tr>
<td>Empirin w/Codeine</td>
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<tr>
<td>Equagesic</td>
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<tr>
<td>Excedrin</td>
</tr>
<tr>
<td>Excedrin Back and Body</td>
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<td>Fasprin</td>
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<tr>
<td>Fiorinal</td>
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<td>Fiorinal w/Codeine</td>
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<td>Fiortal with Codeine Capsules</td>
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<td>Genacote</td>
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<tr>
<td>Gennin-FC</td>
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<td>Genprin</td>
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<td>Goody's</td>
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<tr>
<td>Halfprin</td>
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<tr>
<td>Kaopectate</td>
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<tr>
<td>Levacet</td>
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<tr>
<td>Lobac Capsules and Tablets</td>
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<td>Lortab ASA</td>
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<td>Magan Tablets</td>
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<tr>
<td>Magnaprin</td>
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<tr>
<td>Magsal Tablets</td>
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<tr>
<td>Methocarbamol &amp; Aspirin Tablets</td>
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<td>Methocarbamol w/ASA</td>
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<td>Miniprin</td>
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<tr>
<td>Norgesic Forte</td>
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<tr>
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<tr>
<td>Ridiprin</td>
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<td>Rite Aid Aspirin</td>
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<td>Robaxisal</td>
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<td>Roxiprin</td>
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<td>Saleto</td>
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<tr>
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<tr>
<td>Soma Compound</td>
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<tr>
<td>Soma Compound W/Codeine</td>
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<tr>
<td>St. Joseph</td>
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<td>Stanback Analgesic</td>
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<td>Supac</td>
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<tr>
<td>Synalgos DC</td>
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<tr>
<td>Talwin Compound</td>
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<tr>
<td>Uni-Buff</td>
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<tr>
<td>Uni-Tren</td>
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<tr>
<td>Valomag</td>
</tr>
</tbody>
</table>
Vanquish
Walgreen’s Aspirin

YSP
Zorprin

Store Brand Generics

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