HEMOPHILIA AND VON WILLEBRAND DISEASE EMERGENCIES

ALGORITHM. Hemophilia and von Willebrand Disease Factor Replacement Therapy

Indications for Factor Replacement Therapy
- Suspected bleeding into a joint or muscle
- Any significant injury to the head, neck, mouth or eyes, or evidence of bleeding in those areas
- Any new or unusual headache, particularly one following trauma
- Severe pain or swelling at any site
- All open wounds requiring surgical closure, wound adhesive, or Steri-Strips®
- History of an accident or trauma that might result in internal bleeding
- Any invasive procedure or surgery
- Heavy or persistent bleeding from any site
- Gastrointestinal bleeding
- Acute fractures, dislocations and sprains

Pearls:
- P1: When in doubt, administer clotting factor replacement therapy
- P2: Clotting factor replacement therapy should be infused prior to any labs, radiologic studies, or procedures
- P3: Notify on-call hematologist immediately
- P4: Patient or caregiver’s suspicion of bleeding-related problem is sufficient to initiate factor replacement therapy
- P5: Only order diagnostic tests if they will change the outcome
- P6: Allow patient to use own product
- P7: Patients with factor IX deficiency are at risk for anaphylaxis
- P8: Round dose “up” to the nearest vial size and give the entire vial (do not throw away extra factor) unless Hemophilia A patient weighing less than 5 kg or Hemophilia B patients weighing less than 2 kg

Inclusion Criteria: Diagnosis of Hemophilia
Exclusion Criteria: Patients with Planned Admission

Patient presents to ED

Is factor replacement indicted? (see indications to the left)

Check patient’s problem list for bleed plan documented under Hemophilia Diagnosis or von Willebrand disease

Did patient bring clotting factor?

Pharmacist to verify factor. If pharmacist is not available, nurse to verify at bedside.

Allow patient/caregiver to reconstitute and administer own product.

Off Pathway. Continue care as clinically indicated

What does the patient use at home? If not known, review EHR, see table below for substitutions, and/or consult hematologist.

P: Is preferred product available in pharmacy?

Alert CHCO inpatient pharmacy to order patients preferred product from HTC (303-724-0168) if patient is admitted

Monday-Friday 8am-5pm, factor available within two hours
All other hours, factor available within 4 hours

Initiate factor replacement therapy with preferred product

Initiate factor replacement therapy with substitute CHCO formulary product below (see Table 1 for appropriate substitute):
- If patient needs factor VIII use Advate
- If patient needs factor IX use BeneFIX
- If patient needs factor VIII use w/vWF Humate-P
- If patient needs FEIBA
- If patient needs rFVIIa
- If patient needs dose of DDAVP

If patient is on emicizumab-kxwh please see problem list and consult hematologist.
TABLE OF CONTENTS
Algorithm
Target Population
Clinical Management
Clinical Assessment
Laboratory and Radiology Studies
Therapeutics
Admission Criteria
Discharge Criteria
Follow-Up
Table 1 Product Replacement Guide
Table 2 Desmopressin (DDVAP = CHCO formulary) Dosing
Table 3 Anti-Fibrinolytics
References
Clinical Improvement Team

TARGET POPULATION

Inclusion Criteria

- Patients with a diagnosis of hemophilia or von Willebrand disease and history of injury, complaint of pain, or other concern for bleeding

Exclusion Criteria

- Patients with planned admission

CLINICAL MANAGEMENT

Initial Triage

Triage should be urgent. Delays in administering factor concentrate treatment significantly affect morbidity and mortality in individuals with hemophilia or von Willebrand disease¹

The six major sites for serious bleeding which threaten life, limb, or function are²:

- Intracranial
- Spinal cord
- Throat/mouth
- Intra-abdominal
- Limb compartments
- Ocular

All of the above require immediate assessment and intervention, and are characterized by²
• Bleeding into an enclosed space
• Compression of vital tissues
• Potential loss of life, limb, or function

CLINICAL ASSESSMENT

• Treatment for a suspected bleeding episode is based on clinical history. Many physical exam findings tend to be normal in the early phases of most hemophilic bleeds. Spontaneous bleeding is common in individuals with severe disease. **When in doubt, administer clotting factor replacement therapy**

• Treatment decisions should be based on the **suspicion** of a bleeding-related problem, not a confirmed diagnosis of one.

• If, in their experience, the patient or caregiver suspects occult bleeding is occurring, administer clotting factor replacement. Patients often are instructed in and/or carry with them appropriate factor replacement dosing guidelines as advised by their treating hematologist.

• Consultation with the patient's hematologist or a regional hemophilia treatment center professional is strongly advised; however, this should not delay administration of clotting factor.

Signs and symptoms:

**Head:**
- Early neurological symptoms may not be evident due to the slow, oozing nature of hemophilia bleeding
- Headache with increasing severity
- Irritability
- Vomiting
- Seizures
- Vision problems
- Focal neurological deficits
- Stiff neck
- Altered mental status or change in level of consciousness

**Joint bleeding:**
- Pain
- Restricted movement
- Swelling
- Warmth
- Erythema on and around the joint
- Patient may report symptoms of “bubbling” or “tingling” sensation with no physical signs
- Later symptoms may include:
  - A feeling of fullness within the joint
  - Moderate to severe pain

**Muscle/Soft Tissue bleeding:**
- Any muscle group may be subject to bleeding. Common bleeding sites include upper arm, forearm, thigh, calf muscles, abdominal wall muscles, and iliopsoas muscles
Abdominal muscles generally do not have observable swelling, but may have a palpable mass, rigidity, and pain.

Lower abdominal or groin pain, especially with signs of nerve compression may indicate an iliopsoas bleed.

Other muscles may exhibit:
- Warmth
- Pain
- Swelling

Soft tissue bleeds usually do not require aggressive treatment. Superficial hematomas and bruises may appear anywhere on the body and, if they do not threaten function and mobility, they do not need to be treated.

Gastrointestinal/Urinary Tract bleeding:
- Abdominal pain
- Flank pain
- Hematuria
- Melena
- Vomiting blood
- Dropping hemoglobin
  - Steady dropping hemoglobin may indicate bleed in abdominal cavity
  - Dramatic drop in hemoglobin following trauma may indicate rupture of liver, spleen, or pancreas

Mucous Membrane/Oral bleeding:
- Pain
- Swelling
- Difficulty swallowing
- Difficulty breathing
- Vomiting triggered by swallowed blood
- Patient may report the sensation of postnasal drip (blood running down back of throat from posterior epistaxis) or may report tasting blood

LABORATORY STUDIES | IMAGING
Diagnostic tests are only indicated if they will change outcome.

Clotting factor replacement therapy should be given before any diagnostic studies (radiographs, CT scans etc.) are performed in the evaluation of a suspected bleeding problem, especially in the case of head trauma or suspected intracranial hemorrhage. For routine joint bleeding, no radiographic studies are indicated. If invasive procedure (lumbar puncture, arterial blood gas, arthrocentesis, etc.) or surgery is necessary, factor replacement therapy must be administered in the emergency department beforehand. Factor will be distributed and circulating 15 minutes post IV push.

For an individual with known hemophilia, routine laboratory studies (PT, PTT, factor levels), are not indicated in the treatment of a routine bleeding episode unless requested by the patient’s hematologist. The clinical severity of a patient’s hemophilia is gauged by his or her baseline clotting factor level, a value that remains fairly constant throughout that person’s life.
THERAPEUTICS (SEE TABLES 1, 2, AND 3 FOR DOSING)

- Refer to bleed treatment plan documented in patient’s Problem List under hemophilia diagnosis. A unique plan will be documented in the Problem List for all known hemophilia patients seen by CHCO hematology.
- Most bleeds will require factor replacement except for bruises and minor soft tissue injuries that do not impact function and mobility.
- Treatment for bleeding involves replacing the deficient factor as the first course of action. This requires intravenous infusion of factor concentrates. Specific doses, additional drugs, and medical interventions depend upon the site and severity of bleeding. Once factor replacement therapy has been infused, diagnostic procedures and examinations can begin.
- Goal time (from presentation to ER) for start of administration of factor replacement is 30 minutes or less for suspected head bleeds and 60 minutes or less for suspected bleeding in areas other than the head.
- Indications for factor replacement therapy:
  - Suspected bleeding into a joint or muscle
  - Any significant injury to the head, neck, mouth or eyes, or evidence of bleeding in those areas
  - Any new or unusual headache, particularly one following trauma
  - Severe pain or swelling at any site
  - All open wounds requiring surgical closure, wound adhesive, or Steri-Strips™
  - History of an accident or trauma that might result in internal bleeding
  - Any invasive procedure or surgery
  - Heavy or persistent bleeding from any site
  - Gastrointestinal bleeding
  - Acute fractures, dislocations and sprains

- Considerations for factor replacement therapy:
  - If a patient with hemophilia or the parent of a patient with hemophilia brings clotting factor with them to the emergency department, allow them to use it. The identity and integrity of a patient’s own medication should be verified and documented by a Children’s Hospital Colorado pharmacist prior to administration. In the event a pharmacist is not available to conduct this review promptly, the patient’s own medication may be checked by the nurse caring for the patient. The patient or caregiver should be permitted to reconstitute the product and administer it whenever possible. Individuals with bleeding disorders are encouraged to have an emergency dose of factor concentrate or DDAVP in their home and to take it with them when they travel. In those situations where a patient does not bring their own clotting factor concentrate, emergency departments must be prepared to provide clotting factor replacement. Emergency departments must have ready access to factor replacement products so that they are available within one hour of the patient's arrival.
  - Factor replacement must be administered intravenously by IV push over 1 to 2 minutes.
  - Dose factor up to the "closest vial" by size/assay and infuse the full content of each reconstituted vial. A moderate excess of factor concentrate will not create a hypercoaguable state but will prolong the therapeutic level of the product administered; thus it is prudent to "round up".
  - For individuals with inhibitors (antibodies to factor VIII or IX), treatment decisions may be more complicated. Consult hematology.
  - When treating an individual with mild hemophilia A who is responsive to desmopressin (CHCO formulary = DDAVP), the dose and prior responsiveness are usually known.
The most experienced IV therapist or phlebotomist should perform any venipuncture. Traumatic venipunctures and repeated needle sticks cause painful hematomas that may limit further IV access and lead to compartment syndrome

- Factor infusion kits usually include butterfly needles, which are preferred. If IV access is necessary in otherwise hemodynamically stable patients, the smallest possible gauge needle should be utilized (25g butterfly needles in young infants, 23g butterfly needles in older children and adults)

- In any suspected bleeding emergency in which the clotting factor level of an individual with hemophilia is unknown, the factor level should be assumed to be 0%

- Intramuscular injections should be avoided whenever possible. If they must be given, factor replacement therapy should precede the injection. Parenteral agents should be given intravenously or subcutaneously. Tetanus immunizations may be administered subcutaneously

- Tourniquets should not be applied tightly to extremities because they may cause bleeding

- Analgesics and Antipyretics:
  - Aspirin and aspirin-containing products are contraindicated in individuals with hemophilia
  - Acetaminophen and/or other pain medications (such as morphine or hydrocodone) may be used for analgesia
  - Non-steroidal anti-inflammatory drugs may be carefully administered to select patients, such as individuals with chronic arthritic pain who are not actively bleeding or being treated for a recent bleeding problem

- If an individual with hemophilia is bleeding and requires transportation to another facility for definitive care, all efforts should be made to replace the deficient clotting factor before transport

Hemophilia A without Inhibitor

The treatment of choice for individuals with hemophilia A (factor VIII deficiency) is recombinant factor VIII or the patient’s product of choice. Plasma-derived concentrate is a suitable alternative in an emergency situation when recombinant Factor VIII is not available. See: Hemophilia and von Willebrand Disease Factor Replacement Therapy Algorithm

- When bleeding is severe, the appropriate dose of factor VIII is 50 units/kg. If patient weighs less than 5 kg do not exceed 75 units/kg correction when rounding to vial size (in a patient less than 5 kg you may NOT be able to use the entire vial)
- Cryoprecipitate and fresh frozen plasma are no longer recommended for treatment of individuals with hemophilia A

Mild Hemophilia A with Non-Life or Limb Threatening Bleeding

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

- Desmopressin (CHCO formulary = DDAVP) 1: 0.3mcg/kg subcutaneously
  or
- Desmopressin (CHCO formulary = DDAVP) 1: 0.3mcg/kg diluted in 30 mL normal saline infused over 30 minutes
  or
- Intranasally via ultra-concentrated nasal spray “Stimate”:
  - For patients less than 50 kg: 1 spray in one nostril
  - For patients greater 50 kg: 1 spray in each nostril
Hemophilia B without Inhibitor

The treatment of choice for individuals with hemophilia B (factor IX deficiency) is recombinant factor IX or the patient’s product they usually receive at home. Plasma-derived concentrate, see list of factor IX products in Table 1, is a suitable alternative in an emergency situation when recombinant Factor IX is not available. See: Hemophilia and von Willebrand Disease Factor Replacement Therapy

- Severe factor IX deficient patients are at risk of anaphylaxis and nephrotic syndrome
- Factor IX recovery is unpredictable (often lower recovery) when using BeneFIX®
- If patient treated with BeneFIX® continues to bleed, check a STAT Factor IX activity and redose
- When bleeding is severe, the appropriate dose of factor IX is **120 units/kg**
  - If patient weighs less than 2 kg do not exceed 150 units/kg correction when rounding to vial size (in a patient less than 2 kg you may NOT be able to use the entire vial)
- Fresh frozen plasma is no longer recommended for treatment of individuals with hemophilia B. Note that cryoprecipitate does not contain Factor IX

Hemophilia with Inhibitor

The care of inhibitor patients should be urgently discussed with the patient's hematologist. If an individual with an inhibitor presents in a life- or limb-threatening scenario, the safest immediate action is to prescribe recombinant factor VIII (rFVIII) at a dose of 90 mcg/kg or higher (see patients plan in problem list) activated prothrombin complex concentrates (FEIBA) at 75 units/kg. The patient or family can also provide information on response to therapeutic bypassing agents

- Patients taking Emicizumab-kxwh should not get FEIBA. Please see patient problem list

Note: In factor IX patients with a history of inhibitors and anaphylaxis do not give factor IX-containing products (FEIBA) unless the bleeding is life-threatening

Anti-fibrinolytics

- Anti-fibrinolytics are contraindicated in patients with hematuria
- Aminocaproic Acid:
  - Can be given PO or IV if needed
  - Loading dose: 50 to 200 mg/kg PO or IV every 6 hours for 3 to 10 days. Dose not to exceed 4 grams
  - Maintenance dose: 50-100 mg/kg/dose PO or IV every 6 hours
- Tranexamic Acid (TXA):
  - 1300 mg orally every 8 hours for 5 days10 mg/kg/dose IV every 6 hours or 10 mg/kg/dose IV once to load then 10/mg/kg/hour IV continuous infusion (maximum 1000 mg/dose)

Other Modalities² *(Evidence quality: D)*

1. Protect (bracing)
2. Rest
3. Ice packs
4. Compression (Ace wrap)
5. Elevation
ADMISSION CRITERIA
Discuss admission with hematologist

DISCHARGE CRITERIA
Discuss discharge plan with hematologist. If patient is to be discharged, determine whether or not to leave the port accessed or PIV in place and provided necessary teaching to caregivers

FOLLOW-UP
Notify patient’s hematologist or Hemophilia and Thrombosis Center

<table>
<thead>
<tr>
<th>Table 1. Product Replacement Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product type</strong></td>
</tr>
<tr>
<td>Factor VIII Recombinant</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Factor VIII plasma derived with vWF</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Factor IX Recombinant</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Factor IX plasma derived</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
**CLINICAL PATHWAY**

<table>
<thead>
<tr>
<th>Factor VIII with vWF Complex</th>
<th>Alphanate® (for VWF disease)</th>
<th>Humate-P®</th>
<th>Wilate®</th>
<th>Vonvendi®</th>
<th>Humate-P®</th>
<th>60 VWF:RCo units/kg&lt;sup&gt;×&lt;/sup&gt; (20-80 units/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIIa Recombinant</td>
<td>NovoSeven® RT</td>
<td>NovoSeven® RT</td>
<td></td>
<td></td>
<td></td>
<td>90mcg/kg&lt;sup&gt;×&lt;/sup&gt; (30-270mcg/kg)</td>
</tr>
<tr>
<td>Anti-inhibitor Coagulant Complex</td>
<td>FEIBA NF</td>
<td>FEIBA NF</td>
<td></td>
<td></td>
<td></td>
<td>75 units/kg&lt;sup&gt;×&lt;/sup&gt; (50-85 units/kg)</td>
</tr>
</tbody>
</table>

<sup>×</sup>Refer to patient’s Snapshot in Epic for hemorrhage plan. If available, patient’s hemorrhage plan supersedes dose in this chart

<sup>×</sup>Emicizumab-kxwh is the first in a new class of drugs only for people with hemophilia A. It is a novel bi-specific antibody that bypasses FVIII and allows hemophilia A patient with and without inhibitors have high quality prophylaxis. It is not for treating acute bleeding. The phase 3 clinical trial in adults and children with inhibitors showed efficacy, and its use in non-inhibitor patients is pending FDA approval soon. Complications occurred during the trial, all when trying to treat bleeding. They were thrombosis and thrombotic microangiopathy all associated with the improper use of FEIBA. Because of this FEIBA is contraindicated and to treat bleeding the PI dose of rFVIIa is recommended: 90 mcg/kg/dose. Increasing numbers of patients are starting emicizumab-kxwh. Instructions for treating bleeding are in the Problem List and the Hematologist on call should be notified when treating a patient on emicizumab-kxwh

**Table 2. Desmopressin (DDVAP = CHCO formulary) Dosing**

<table>
<thead>
<tr>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneously</td>
<td>0.3mcg/kg subcutaneously</td>
</tr>
<tr>
<td>Intravenously</td>
<td>0.3mcg/kg diluted in 30 mL normal saline infused over 30 minutes</td>
</tr>
</tbody>
</table>
| Intranasally via ultra-concentrated nasal spray "Stimate" | For patients less than 50 kg: 1 spray in one nostril  
For patients greater 50 kg: 1 spray in each nostril |
Table 3. Anti-fibrinolytics
Note: Anti-fibrinolytics are contraindicated in patients with hematuria

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminocaproic Acid (ACA)</td>
<td><strong>Loading dose</strong>: 50 to 200 mg/kg orally or IV every 6 hours for 3 to 10 days.</td>
</tr>
<tr>
<td></td>
<td>Dose not to exceed 4 grams</td>
</tr>
<tr>
<td></td>
<td><strong>Maintenance dose</strong>: 50-100 mg/kg/dose orally or IV every 6 hours</td>
</tr>
<tr>
<td>Tranexamic Acid (TXA)</td>
<td><strong>Oral</strong>: 1300 mg orally every 8 hours for 5 days</td>
</tr>
<tr>
<td></td>
<td><strong>IV</strong>: 10 mg/kg/dose IV every 6 hours or 10 mg/kg/dose IV once to load then 10/mg/kg/hour IV continuous infusion</td>
</tr>
</tbody>
</table>
REFERENCES


2. Emergency Care for Patients with Hemophilia. Third ed: Clarence Printing; 2010


Clinical pathways are intended for informational purposes only. They are current at the date of publication and are reviewed on a regular basis to align with the best available evidence. Some information and links may not be available to external viewers. External viewers are encouraged to consult other available sources if needed to confirm and supplement the content presented in the clinical pathways. Clinical pathways are not intended to take the place of a physician's or other health care provider's advice, and is not intended to diagnose, treat, cure or prevent any disease or other medical condition. The information should not be used in place of a visit, call, consultation or advice of a physician or other health care provider. Furthermore, the information is provided for use solely at your own risk. CHCO accepts no liability for the content, or for the consequences of any actions taken on the basis of the information provided. The information provided to you and the actions taken thereon are provided on an "as is" basis without any warranty of any kind, express or implied, from CHCO. CHCO declares no affiliation, sponsorship, nor any partnerships with any listed organization, or its respective directors, officers, employees, agents, contractors, affiliates, and representatives.
Discrimination is Against the Law. Children's Hospital Colorado complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Children's Hospital Colorado does not exclude people or treat them differently because of race, color, national origin, age, disability, or sex.

Children's Hospital Colorado provides free aids and services to people with disabilities to communicate effectively with us, such as: Qualified sign language interpreters, written information in other formats (large print, audio, accessible electronic formats, other formats). Children's Hospital Colorado provides free language services to people whose primary language is not English, such as: Qualified interpreters, information written in other languages.

If you need these services, contact the Medical Interpreters Department at 720.777.9800.

If you believe that Children's Hospital Colorado has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with: Corporate Compliance Officer, 13123 E 16th Avenue, B450, Aurora, Colorado 80045, Phone: 720.777.1234, Fax: 720.777.7257, corporate.compliance@childrenscolrado.org. You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Corporate Compliance Officer is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at ocrportal.hhs.gov/portal/lobby.jsf, or by mail or phone at U.S. Department of Health and Human Services 200 Independence Avenue, SW Room 509F, HHH Building Washington, D.C. 20201 1-800-368-1019, 800-537-7697 (TDD) Complaint forms are available at www.hhs.gov/ocr/office/index.html.

Children's Hospital Colorado complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex.

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 1-720-777-9800.


注意: 如果您使用繁體中文，您可以免費獲得語言援助服務。請致電1-720-777-9800。

ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните по 1-720-777-9800.

Melhorada: ka kanitsi la ante k'ene, mali muboroom yafe, yaelu, ka 720-777-9800.


注意事項: 日本語を話される場合、無料の言語支援をご利用いただけます。1-720-777-9800 まで、お電話にてご連絡ください。