Evidence-Based Emergent Management Of Bleeding Disorders

Abstract

Children with both congenital (eg, hemophilia or von Willebrand disease) and acquired (eg, immune thrombocytopenia [ITP]) bleeding disorders frequently present to the emergency department (ED) with a wide variety of bleeding-related problems ranging from petechiae to intracranial hemorrhage (ICH). In many instances, such as hemophilia or von Willebrand disease, the bleeding disorder has been previously diagnosed because of an abnormal family history or bleeding in infancy. However, in other instances, a patient may present with abnormal bleeding symptoms (such as a patient with ITP), and it is the role of the emergency clinician to facilitate the diagnosis and initiate therapy.

This Pediatric Emergency Medicine Practice article provides up-to-date guidelines and an evidence-based review of the most common bleeding disorders and management of specific bleeding emergencies in the ED.

Case Presentation

A 5-year-old girl with type 3 von Willebrand disease presents to the ED with epistaxis after a forceful sneeze. It has not resolved after 30 minutes of direct pressure. You recall that most patients with von Willebrand disease have mild symptoms such as easy mucosal bleeding, but this patient is still bleeding profusely out of both nares and is beginning to look pale with

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mild tachycardia. You’re surprised by the severity of the patient’s presentation and wish you were more familiar with the types of von Willebrand disease.

Your next patient is an 18-month-old boy with hemophilia brought to the ED after falling down 6 steps. He has an occipital scalp hematoma but is otherwise well appearing. His family is new to the area and does not have a primary care provider currently.

Your colleague signs out a 4-year-old child with presumed ITP who is receiving WinRho® in room 7 in an effort to manage the child on an outpatient basis. Shortly after your colleague leaves, you are called to the room because the patient has rigors and a temperature of 104°F (40°C).

Critical Appraisal Of The Literature

Ovid MEDLINE® and PubMed were searched for literature (published from 1960 to the present) on bleeding disorders with a focus on pediatric patients. Terms used in the search included but were not limited to: bleeding disorder, coagulation disorder, ITP, idiopathic thrombocytopenia, immune thrombocytopenia, hemophilia, and von Willebrand disease. The National Guideline Clearinghouse (www.guidelines.gov) and the Cochrane Database of Systematic Reviews as well as the websites of the American Society of Hematology (http://www.hematology.org/PracticeGuidelines) and British Society for Hematology (http://www.bcsgh guidel ines.com) were consulted.

Although the body of literature examining the risks and management of emergent bleeding disorders is large, published data is primarily from case series and prospective and retrospective cohort observational studies. Multiple consensus guidelines are available for more common disorders (eg, hemophilia A and B, von Willebrand disease, and ITP), but many of the recommendations are based on expert opinion.1-11 (See Table 1.) While several randomized controlled trials have compared specific therapies or compared an individual therapy to observation or placebo,12-17 much of the data supporting individual therapies for hemophilia and von Willebrand disease are derived from open-label prospective cohort studies. These outcome measures are often subjective, such as the assessment of therapeutic response as “excellent,” “good,” or “poor.”18-43

Similar limitations may be found within the body of evidence regarding management of ITP. Investigations of ITP often use platelet count as a surrogate marker of effective therapy. However, no study adequately demonstrates a specific platelet count that is directly correlated with bleeding risk and clinical outcome. As with other bleeding conditions, the preponderance of the evidence is derived from prospective cohorts and case series. A few well-designed randomized trials have provided direct comparisons between therapeutic options, but these suffer from small sample sizes.44-52

Epidemiology, Etiology, And Pathophysiology

In healthy individuals, hemostasis is achieved by intricate interrelated mechanisms involving the vascular endothelium, platelets, and coagulation factors. The coagulation cascade involves multiple procoagulant proenzymes circulating in the blood. These proenzymes are synthesized in the liver and, in their active forms, help produce thrombin from its precursor, prothrombin.

The clotting cascade is classically described as consisting of extrinsic and intrinsic pathways, each merging into a common pathway. The intrinsic pathway is triggered by contact between blood (factor XII, kallikrein) and damaged subendothelium (collagen). Activated factor XII cascades through factor XI and factor IX (with its cofactor, factor VIII) into the common pathway, converting factor X into factor Xa. Tissue factor, released by damaged endothelium, initiates the extrinsic pathway by activating factor VII, which in turn causes the conversion of factor X to factor Xa.

In the common pathway, factor Xa (in conjunc-
tion with its cofactor, factor V) converts prothrombin (factor II) to thrombin. Finally, thrombin cleaves fibrinogen into fibrin monomers that assemble into fibrin fibers. Thrombin also facilitates the release of von Willebrand factor from circulating von Willebrand factor/factor VIII complex, making it available for platelet activation and aggregation. (See Figure 1)

When the vascular endothelium sustains an injury, von Willebrand factor is also secreted. Von Willebrand factor, synthesized in megakaryocytes and endothelial cells, binds to platelet surface receptors (Ib) and facilitates platelet activation and adhesion to exposed subendothelial collagen matrix. Platelets then undergo shape changes that allow GPIIb/IIIa receptors on activated platelets to bind to fibrinogen, resulting in a stable clot.

**Specific Bleeding Disorders**

**Platelet Disorders**

Platelet disorders can be divided into 2 main categories, quantitative thrombocytopenia and functional platelet dysfunction. (See Table 2 on page 4.) Quantitative thrombocytopenia is defined as a platelet count less than 150,000/mm³. Thrombocytopenia, in turn, can be caused by decreased production or increased destruction of platelets. Platelet production may be impaired by infection, nutritional deficiencies, malignancy, or from rare congenital (genetic) disorders. Many of these conditions (eg, leukemia) are associated with abnormalities in other cell lines.

Immune thrombocytopenia is the most common cause of isolated thrombocytopenia. While ITP is defined as a platelet count of less than 100,000/mm³, more than 50% of patients with ITP will present with platelet counts below 20,000/mm³. Immune thrombocytopenia is thought to be the result of antibody-mediated platelet destruction within the reticuloendothelial system (primarily in the spleen). More recently, impaired platelet production and T-cell-mediated platelet destruction have been recognized as additional contributors.

Children with ITP most often present with small petechiae and bruising, but a lesser number may also have mucosal bleeding such as epistaxis, bleeding from the mouth, or bleeding in the gastrointestinal tract. The number of children presenting with severe bleeding episodes requiring hospital admission and/or blood transfusions during the first 28 days of illness has been estimated to be as low as 2.9%. Intracranial hemorrhage is the feared complication of ITP, but it has a very low reported incidence (0.19%-0.78%). Seventy-five percent of patients with ICH have platelet counts below 10,000/mm³. The incidence of ITP peaks around 2 to 5 years of age, and data from case series demonstrates that over 70% of children with ITP will have recovered within 6 months.

**Coagulation Disorders**

**Hemophilia**

A deficiency of any component of the coagulation cascade, congenital or acquired, can cause a bleeding disorder. The most common inheritable conditions
are factor VIII deficiency (hemophilia A) and factor IX deficiency (hemophilia B). These 2 X-linked disorders have an incidence of 1:10,000 and 1:60,000, respectively.\(^6^1\) Congenital deficiencies of other coagulation factors (fibrinogen, prothrombin, factor VII, factor X, factor XI, factor XIII) are autosomal recessive and are much less common.\(^6^1\) Subsequent discussion will focus on factor VIII and factor IX deficiencies.

The severity of factor VIII and factor IX deficiencies is determined by the factor activity level: mild (5%-40%), moderate (1%-5%), and severe (< 1%).\(^6^2\) Severe hemophilia comprises the largest group.\(^6^3\) In the newborn period, children with hemophilia may present with ICH or with excessive bleeding after circumcision or heel stick blood sampling.\(^6^4\) Children with severe hemophilia are more likely to experience spontaneous hemarthroses, intramuscular hematomas, and difficult-to-control bleeding from lacerations or oral lesions.

Most children experience their first significant bleeding episode during the toddler years. One prospective study of 37 children observed that approximately 44% of children with hemophilia had their first bleeding episode of any type by the age of 1 year and their first episode of hemarthrosis at a mean age of 1.9 years.\(^6^7\) A retrospective analysis of 126 pediatric ED visits for hemophilia demonstrated that 48% of visits were for soft-tissue hematomas, 24% for hemarthroses, and 12% for head injuries.\(^6^8\)

Recurrent hemarthrosis is the most serious chronic morbidity. Blood in the joint provokes an intense inflammatory cascade that results in synovial revascularization, enhanced vulnerability to recurrent bleeding, and eventually, cartilage destruction. The ankle is the most commonly affected joint in children, but other affected joints include the knee, elbow, and shoulder. Prophylactic factor administration beginning at a young age is an aggressive approach to interval treatment that has significantly reduced the development of hemophilic arthropathy.

Intramuscular hematomas can be incredibly painful and may result in significant neurovascular morbidity (eg, compartment syndrome, nerve compression). Iliopsoas hematoma may be especially difficult to diagnose, frequently mimicking acute appendicitis or hip pathology. Pain may be especially severe if there is compression of the femoral nerve or sacral plexus. Less common bleeding manifestations include hematuria, intracranial or intraocular hemorrhage, gastrointestinal bleeding, or intestinal hematoma.

Intracranial hemorrhage has exceeded HIV as the leading cause of death in hemophilia patients.\(^6^9\) Intracranial hemorrhage can occur with or without a history of trauma and is much more likely to occur in patients with severe hemophilia. In a French study, only 62% of patients younger than 15 years reported a history of trauma;\(^6^6\) diagnosis was delayed in 43% of these patients, and treatment was delayed in 37%. It is possible that “spontaneous” ICH really represents minor, unrecognized trauma from days before.\(^6^9\)

### Von Willebrand Disease

Although hemophilia is the most well-known coagulation disorder, von Willebrand disease is far more common, with an estimated prevalence of 0.8% to 1.3% of the general population.\(^7^0,7^1\) In contrast to hemophilia, mucocutaneous bleeding characterizes von Willebrand disease.\(^3\) Patients with clinically significant von Willebrand disease typically experience heavy menses, recurrent or prolonged epistaxis, gingival or intraoral bleeding, easy bruising, and post-procedural bleeding.\(^7^2-7^4\)

Unlike many other coagulation factors, von Willebrand factor has no enzymatic activity. Von Willebrand factor is a large multimeric protein which functions as a binding protein; it facilitates the binding of activated platelets to exposed subendothelial collagen as well as platelet-to-platelet clumping (through the glycoprotein Ib receptor). Von Wil-

### Table 2. Platelet Disorders

<table>
<thead>
<tr>
<th>Impaired Platelet Production</th>
<th>Platelet Destruction</th>
<th>Platelet Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Infection with bone marrow suppression (eg, HIV, parvovirus)</td>
<td>• Immune thrombocytopenia</td>
<td>• Platelet-vessel wall adhesion defects (eg, Bernard-Soulier syndrome)</td>
</tr>
<tr>
<td>• Leukemia</td>
<td>• Neonatal alloimmune thrombocytopenia</td>
<td>• Platelet-platelet interaction defects (eg, Glanzmann's thrombasthenia)</td>
</tr>
<tr>
<td>• Nutritional deficiencies (eg, vitamin B12, folate)</td>
<td>• Sequestration from hypersplenism (eg, malaria)</td>
<td>• Acquired platelet dysfunction</td>
</tr>
<tr>
<td>• Medications (eg, NSAIDs, aspirin)</td>
<td>• Platelet consumption (eg, Kasabach-Meritt, disseminated intravascular coagulation, hemolytic-uremic syndrome)</td>
<td></td>
</tr>
<tr>
<td>• Congenital disorders (eg, Wiscott-Aldrich syndrome, thrombocytopenia with absent radius,)</td>
<td>• Medication (eg, heparin-induced thrombocytopenia, trimethoprim/sulfamethoxazole)</td>
<td></td>
</tr>
<tr>
<td>• Infection with bone marrow suppression (eg HIV, parvovirus)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs.

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lebrand factor also provides a critically important function as a carrier protein for factor VIII, slowing its otherwise rapid clearance from the blood.

Von Willebrand disease can be divided into 3 primary types. Autosomal dominant type 1 affects about 75% of patients with von Willebrand disease. Heterozygous carriers have a mild quantitative deficiency of von Willebrand factor, resulting in mild-to-moderate mucocutaneous bleeding. These patients may have such mild clinical manifestations that they escape detection throughout their lives. Type 2 von Willebrand disease consists of a collection of qualitative defects in von Willebrand factor with variable bleeding severity. Patients with type 2N have impaired binding of von Willebrand factor to factor VIII, resulting in clinical features similar to hemophilia A due to rapid clearance of unbound factor VIII from the blood stream. Type 2, the most severe form of von Willebrand disease, is rare and is characterized by an almost complete deficiency of von Willebrand factor (and extremely low levels of factor VIII), leading to severe bleeding complications, including ICH in up to 8% of patients.

Acquired Coagulopathies

A variety of conditions may result in secondary (or acquired) coagulopathies, including vitamin K deficiency, warfarin ingestion, liver disease, disseminated intravascular coagulation (DIC), and acquired factor inhibitors. (See Table 3.)

Hemorrhagic disease of the newborn (HDN), a result of severe vitamin K deficiency, is seen in the neonatal period. Because vitamin K is essential for the production of functioning clotting factors II, VII, IX, and X, vitamin K deficiency can cause a severe bleeding diathesis. Newborns are at particular risk of vitamin K deficiency because they have low stores of vitamin K and receive only minimal amounts via breast milk. Bleeding can occur from multiple sites within 2 to 5 days of delivery, including the umbilicus, mucus membranes, circumcision, and intracranially. Intracranial hemorrhage accounts for the relatively high morbidity and mortality associated with this condition. Late disease may present between 2 to 12 weeks of age. Universal prophylactic neonatal vitamin K supplementation has virtually eliminated this disease except in patients who decline or miss vitamin K administration for personal reasons such as home deliveries.

Ingestion of warfarin may cause coagulopathy by interfering with the hepatic production of vitamin K-dependent coagulation factors. In addition to its therapeutic use as an anticoagulant, warfarin and superwarfarins are also contained in commonly used rodenticides; 87% of the reported 10,157 pediatric warfarin exposures in the United States in 2008 were secondary to rodenticide exposure. Fortunately, the majority of rodenticide exposures involve minimal quantities that do not result in overt coagulation abnormalities.

In contrast to liver failure, in which coagulation factors are underproduced, DIC results from rapid depletion by systemic activation of the coagulation system. Most commonly associated with sepsis, DIC can also be caused by a variety of insults, including trauma, malignancy, Kasabach-Meritt syndrome, and infections. Diffuse intravascular thrombosis of small and mid-size vessels results in end-organ damage and paradoxical hemorrhage from massive consumption of coagulation factors.

Acquired factor inhibitors can result in a significant bleeding diathesis. IgG4 autoantibodies that bind and inactivate factor VIII have been the most studied and occur most commonly in patients who receive multiple factor replacement infusions (which are subsequently recognized as foreign antigens). Inhibitors may also be seen with autoimmune and collagen vascular disease, malignancy, and viral infection. Antibody formation to other coagulation factors may also occur in acquired von Willebrand

Table 3. Differential Diagnosis Of Common Bleeding Disorders

<table>
<thead>
<tr>
<th>Platelet Problems</th>
<th>Inherited Coagulation Disorder*</th>
<th>Acquired Coagulation Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Thrombocytopenia</td>
<td>• Hemophilia A (factor VIII deficiency)</td>
<td>• Vitamin K deficiency</td>
</tr>
<tr>
<td>• Platelet dysfunction</td>
<td>• Hemophilia B (factor IX deficiency)</td>
<td>• Toxic ingestions (eg. warfarin)</td>
</tr>
<tr>
<td></td>
<td>• Von Willebrand disease</td>
<td>• Liver disease</td>
</tr>
<tr>
<td></td>
<td>• Fibrinogen deficiency</td>
<td>• Disseminated intravascular coagulopathy</td>
</tr>
<tr>
<td></td>
<td>* Congenital gene mutations of any factor (including factors II, VII, VIII, IX, X, XI, XII) in the coagulation cascade may result in phenotypic expression as a coagulation disorder</td>
<td></td>
</tr>
</tbody>
</table>

* Congenital gene mutations of any factor (including factors II, VII, VIII, IX, X, XI, XII) in the coagulation cascade may result in phenotypic expression as a coagulation disorder
disease which is seen in patients with lymphoproliferative disorders, neoplasia (ie, Wilms tumor), and autoimmune disorders.  

**Prehospital Care**

Prehospital care of the patient with a bleeding disorder should focus on the management of life-threatening problems. Direct pressure should be placed on lacerations or other sites of potential exsanguination, and injured extremities should be immobilized. Ideally, prehospital providers will identify what therapeutic agents each individual patient might require such as specific factor replacement products. This information will expedite care in the ED, and many patients are able to provide these products prior to transport.

**Emergency Department Evaluation**

**History**

In a patient with a known bleeding disorder, it is critical to accurately identify the disorder before administering therapeutic agents. This may seem self-evident, but a patient’s family may not be perfectly clear about which factor is deficient. If a patient has hemophilia, ask if they know which replacement product they usually receive. They will often bring their factor concentrate with them to the ED, since many hematologists will prescribe doses of the proper replacement agent in advance.

Patients with bleeding disorders may present with a wide variety of acute complaints. (See Table 4.) Spontaneous hemarthrosis is the most common nontraumatic bleeding condition in hemophilia, and initial premonitory symptoms are not clinically overt. Burning, tingling, or prodromal stiffness should be taken seriously, should be considered early evidence of joint hemorrhage, and should prompt urgent factor replacement, regardless of the clinical examination. Likewise, limb pain without the clear presence of joint pathology should prompt the consideration of intramuscular hematoma. Iliopsoas (and retroperitoneal) bleeding can be difficult to diagnose clinically. Discomfort may mimic acute appendicitis or renal colic with radiation to the flank. Compression of the femoral or sacral nerve plexus by iliopsoas hematoma may produce radicular radiation down the lower extremity.

Significant headache, even in the absence of clear head trauma, must be taken seriously as ICH is the number one life-threatening condition for hemophiliacs.

A careful medication history may identify medicines such as aspirin or nonsteroidal anti-inflammatory drugs that can cause significant platelet dysfunction in predisposed individuals. Current or recent heparin administration is known to cause drug-induced thrombocytopenia in addition to therapeutic anticoagulation. Presumably, patients with toxic warfarin or rodenticide ingestion will provide this information.

Current medical problems such as known liver failure or renal insufficiency can help identify patients at risk for bleeding diathesis. Immunodeficient patients are at risk for sepsis and DIC. Oozing from umbilical or circumcision sites may be a clue to severe vitamin K deficiency in neonates born outside of the hospital. Any bite by an unidentified snake should be considered to pose a risk of venom-mediated coagulopathy.

Identifying patients with a previously undiagnosed bleeding disorder who require further hematologic evaluation can be difficult. Children with recurrent, moderately severe epistaxis and normal labs (ie, prothrombin time [PT]/partial thromboplastin time [PTT]) and adolescent females presenting with menorrhagia are potential candidates for a hematology referral and further work up. A history of heavy or prolonged menses, easy bruising, or excessive bleeding after dental procedures will help to guide the emergency clinician towards subspecialty referral. Specific historical elements that are predictive of a bleeding disorder are listed in Table 5.

**Physical Examination**

The initial focus in the patient with a known or suspected bleeding disorder is on vital signs and circulatory status. Tachycardia, with or without hypotension, is a sign of hypovolemia and shock in an actively bleeding patient. The presence of altered mental status must be determined quickly to determine whether the patient has signs of advanced shock or unrecognized ICH. Fever may be a clue to underlying sepsis and DIC.

Patients with various bleeding disorders will ex-

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**Table 4. Common Acute Complaints**

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Etiology</th>
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<tbody>
<tr>
<td>Abdominal or flank pain</td>
<td>Retroperitoneal bleeding, iliopsoas hematoma</td>
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<tr>
<td>Muscle pain</td>
<td>Intramuscular hematoma</td>
</tr>
<tr>
<td>Premonitory symptoms: warmth, burning, stiffness or tingling in joint</td>
<td>Hemarthrosis</td>
</tr>
<tr>
<td>History of minor head trauma, altered mental status</td>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>Headache without trauma</td>
<td>Intracranial bleeding</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Anterior or posterior nosebleed</td>
</tr>
<tr>
<td>Bleeding from mouth</td>
<td>Bleeding from oral mucosa</td>
</tr>
<tr>
<td>Rash/skin problem</td>
<td>Petechiae, ecchymoses</td>
</tr>
<tr>
<td>Eye pain, visual changes</td>
<td>Intraocular bleeding</td>
</tr>
<tr>
<td>Back pain, weakness</td>
<td>Intraspinal hematoma</td>
</tr>
<tr>
<td>Dark urine</td>
<td>Hematuria</td>
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</table>
perience complications that vary by system, identifiable on examination. A careful head and neurologic examination is critical for any patient who has any history of head injury or headache. Any external evidence of head injury in the presence of altered mental status or headache is of great concern. Additionally, altered mental status with a history of minor head trauma, even with an otherwise normal examination, should be considered ICH until proven otherwise. For the patient with epistaxis, the location of bleeding (anterior versus posterior) should be identified. For any patient with a suspected bleeding disorder and history of trauma, any swelling in the oropharynx or neck must be addressed immediately because hemorrhage and expanding hematoma may cause airway compromise.

An abnormal pulmonary examination may be due to pulmonary hemorrhage and is most likely to be seen in entities such as HDN. The presence of hepatosplenomegaly in a patient with thrombocytopenia suggests a diagnosis other than ITP. Abdominal tenderness and or distension may be seen in such bleeding-related conditions as intestinal hematoma or iliopsoas hematoma. However, it is important to recognize that patients with coagulation defects can also suffer from more common conditions, such as acute appendicitis.

The presence of swollen or tender joints or muscles or pain with range of motion suggests the presence of hemarthrosis or muscular hematoma. Pain elicited with movement of the extremity but without visible joint effusion is suggestive of muscular hematoma. However, a normal examination should not dissuade the clinician from providing factor replacement for hemarthrosis in children with suggestive complaints. Pain with hip extension without concurrent, equivalent pain with hip rotation suggests iliopsoas hematoma rather than pathology within the hip joint.

The skin examination may provide clues as to the presence of a coagulation defect in patients without a preceding formal diagnosis. Petechiae (pinpoint, unraised, round, non-blanching, red spots under the skin) suggest platelet problems such as thrombocytopenia or platelet dysfunction. In well-appearing patients, purpura (small palpable hemorrhages in the skin) may be indicative of a vasculitic disorder (eg, Henoch-Schönlein Purpura) but may also be found with platelet problems such as ITP. Large ecchymoses or prolonged bleeding from lacerations and abrasions are more commonly noted in patients with coagulation defects such as von Willebrand disease or hemophilia. In ill-appearing patients, the diagnosis of possible severe sepsis and DIC must be aggressively pursued.

### Diagnostic Studies

It is important to initiate therapy in patients with acute symptoms and not wait for diagnostic studies. Replacement therapy should be rapidly administered prior to sending the patient for radiographic studies.

### Laboratory Testing

Laboratory testing in the ED must focus on tests that produce results quickly and inform the emergent management of the patient. In the ED, this generally means a complete blood count (CBC) with peripheral smear, PT and activated partial prothromboplastin time (aPTT), and type and screen (when indicated).

A CBC will determine whether a quantitative platelet problem is present. Of note, ethylenediaminetetraacetic acid (EDTA)-related pseudothrombocytopenia can occur when blood samples from predisposed individuals are stored with EDTA. This phenomenon has no in-vivo clinical significance except that it may misdirect the unaware practitioner. The hemoglobin and hematocrit will provide evidence of anemia and also establish a baseline for a patient with ongoing bleeding. In actively bleeding patients, values may lag behind clinical severity and should be interpreted with care. Abnormalities in more than 1 cell line may indicate the presence of a malignancy such as leukemia or lymphoma, even in the absence of diagnostic blasts on the peripheral smear.

The PT and aPTT will test for gross abnormalities in the coagulation pathways. Isolated elevation of the aPTT is the sine qua non of hemophilia; functional defects of the intrinsic arm of the coagulation cascade, proximal to the common pathway, will manifest as an elevated aPTT in the face of a normal PT. Both factor VIII and factor IX deficiencies should demonstrate this pattern. Less commonly, isolated elevation of the PT suggests an abnormality of the extrinsic pathway, such as factor VII. Simultaneous elevation of both tests suggests a defect in the common pathway such as factors II and X or severe derangements in the entire coagulation cascade, such as DIC. Patients with DIC will often have alterations in other tests such as a platelet count of < 100,000/mm³ and the presence of fibrin-degradation products.

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**Table 5. Historical Predictors Of Potential Bleeding Disorder**

- Presence of bleeding disorder in a family member
- Abnormal bleeding after trauma (not including birth)
- Post-surgical bleeding
- Prolonged bleeding after tooth extraction
- Menorrhagia
- Prolonged bleeding after circumcision
- Cephalohematoma at time of birth
- Hematuria (macroscopic or microscopic)
- History of transfusions, recent chemotherapy
A type and screen should be sent on any patient with a suspected or known bleeding disorder who may require a transfusion of blood products. In patients with ITP, Rh testing is necessary in patients who might receive anti-Rho(D) antibodies as part of their treatment. Further testing including renal function tests, liver function tests, and thyroid function tests may be useful to determine causes of bleeding disorders such as uremia, liver failure, and thyroid disease. Fibrinogen and fibrinogen degradation product tests are part of the DIC panel. A urine analysis may be useful to confirm suspected microscopic or macroscopic hematuria.

Additional testing, including a von Willebrand disease screen (consisting of factor VIII levels, von Willebrand factor antigen and ristocetin cofactor assay [ristocetin mediates von Willebrand factor-platelet binding in vitro]) may be useful to facilitate diagnosis. Additionally, hematologists may request evaluation for the presence of factor inhibitors in patients who do not have the expected response to therapy. However, these tests will not be available at the time of the visit and should only be ordered in consultation with a hematologist who can interpret and follow-up results.

**Radiologic Testing**

While joint radiographs may demonstrate chronic changes of hemophilic arthropathy, such as joint space narrowing, epiphyseal overgrowth, and widened intercondylar notches, they are unnecessary in the acute management of spontaneous hemorrhage. While hemorrhage should be treated clinically, radiographs may help to differentiate acute fracture from hemarthrosis or muscular hematoma in a ten-

| Table 6. Interpretation Of PT And aPTT Results |
|-----------------|-----------------|-----------------|
| PT and aPTT | Specific Bleeding Disorders | Coagulation Pathway |
| Normal PT | Von Willebrand disease, platelet function problem | Not a problem with coagulation cascade |
| Normal PT, ↑ aPTT | Factor deficiency (VIII, IX, XI, or XII); lupus anticoagulant | Intrinsic pathway |
| ↑ PT, Normal aPTT | Factor VII deficiency | Extrinsic pathway |
| ↑ PT, ↑ aPTT | DIC, sepsis, liver disease, Kasabach-Merritt syndrome, heparin, factor deficiency (II, V, X), fibrinogen deficiency | Both intrinsic and extrinsic pathways or common pathway |

Abbreviations: DIC, disseminated intravascular coagulation; PT, prothrombin time; aPTT, activated partial thromboplastin time

When hemarthrosis should be treated clinically, while joint radiographs may demonstrate chronic changes of hemophilic arthropathy, such as joint space narrowing, epiphyseal overgrowth, and widened intercondylar notches, they are unnecessary in the acute management of spontaneous hemorrhage. While hemorrhage should be treated clinically, radiographs may help to differentiate acute fracture from hemarthrosis or muscular hematoma in a ten-

**Sonography** may be useful when evaluating a patient with a bleeding disorder and suspected intraocular hemorrhage, hemarthrosis, and/or soft-tissue hematomas. Although not specifically studied in hemophilia, ultrasonography allows for noninvasive and rapid assessment of vitreous hemorrhage. Ultrasonography can also be used to identify joint effusions (eg, hip) and provides an alternative to computed tomography (CT) scan for the evaluation of patients with potential iliopsoas hemorrhage, although data on this subject is limited to case series and retrospective reviews.

A CT scan is an excellent modality to assess iliopsoas hemorrhage or other retroperitoneal lesions and may be necessary when ultrasound findings are equivocal or unavailable. A CT scan of the abdomen/pelvis should be considered in any patient with a bleeding disorder and lower abdominal or hip pain.

The diagnosis of ICH in children with bleeding disorders can be facilitated by a CT scan. However, in the well-appearing child with a normal examination, there are no clear guidelines on when a head CT is clinically indicated. Even among pediatric hematologists, there is wide variation regarding the use of head CT imaging for a well-appearing hemophiliac who has sustained a minor head injury.

One retrospective cohort of 97 pediatric patients with hemophilia (A and B) found that of 295 head CT scans performed for minor head injury, 9 cases of ICH were identified; a lack of symptoms and a normal neurologic examination did not exclude ICH. Another review of 43 patients followed over 9 years, with 73 presentations of patients suspected to have ICH upon arrival in the ED, demonstrated 4 risk factors for ICH: severe phenotype, absence of maintenance prophylaxis, presence of a factor inhibitor, and altered level of consciousness at presentation. In particular, the authors found that the absence of altered consciousness had a 98% negative predictive value for ICH (67% positive predictive value). Unfortunately, these findings have not been confirmed in other patient groups and have not been reproduced prospectively. In the ED, a conservative approach should be taken: after emergent factor replacement, a CT scan should always be performed on patients with any neurologic examination abnormality or alteration in consciousness, with strong consideration for imaging children with hemophilia who present with minor head injury. The threshold for what constitutes a “severe” enough minor head injury to warrant imaging is obviously a matter of clinical judgment.

Also, because of the susceptibility to spontaneous or traumatic ICH, a head CT should be performed on any patient with ITP, low platelets, and headache with abnormal neurologic examination,
and/or minor head injury. One case-control study and several case series and retrospective analyses have been performed that examine risk for ICH.\textsuperscript{5,111-114} Psaila et al conducted a nationwide survey over 13 years and estimated a population-based incidence of ICH of 0.19% to 0.78%.\textsuperscript{35} Of the children with ICH, 90% had platelet counts less than 20,000/mm\textsuperscript{3}, and 75% had platelet counts less than 10,000/mm\textsuperscript{3}.\textsuperscript{35} Any concomitant bleeding other than petechiae and ecchymosis was predictive of ICH. A retrospective investigation performed by Elalfy et al of 1840 patients with ITP identified 10 cases of ICH. Of these 10 patients, 7 had platelet counts of less than 1,000/mm\textsuperscript{3}.\textsuperscript{112} Only 1 patient had a history of head trauma. A second retrospective analysis by Choudhary et al of 750 patients with ITP, aged 10 months to 18 years, identified 17 cases of ICH.\textsuperscript{113} Only 4 cases were precipitated by head trauma. The median platelet count in these patients was 12,000/mm\textsuperscript{3} (range: 2000/mm\textsuperscript{3} - 50,000/mm\textsuperscript{3}).

Magnetic resonance imaging should be used to assess suspected spinal epidural hematomas in patients with hemophilia but only after factor replacement is given.\textsuperscript{94,115-118} Magnetic resonance imaging is also excellent for detecting abnormal changes associated with hemarthroses but is not indicated for this purpose in the emergency setting.\textsuperscript{101,119}

**Therapy**

**Emergent Therapy For Congenital Bleeding Disorders**

Emergency management of hemorrhage for patients with a congenital bleeding disorder centers on increasing the circulating levels of deficient clotting factors. This discussion focuses on the treatments of factor VIII and IX deficiencies and von Willebrand disease. Many clinical trials have been performed, but almost all of these are open-label and non-randomized. In addition, no head-to-head comparisons of the most commonly used therapeutic agents have been published. In a large number of studies examining factor replacement products, the primary outcome was the investigators’ (subjective) assessment of whether the patient's response was “excellent/good.”

Several guidelines based on evidence and expert consensus have been published to assist with the management of hemorrhage in patients with congenital bleeding disorders.\textsuperscript{3-7} All of these guidelines highlight that rapid correction of deficient clotting factors is tantamount. Specific replacement products should be used if available and are discussed in the following section. If unavailable, cryoprecipitate (for factor VIII deficiency) or fresh frozen plasma (FFP) (for factor IX deficiency) may be used as a last resort. The goal of factor replacement is generally considered to be 40%-50% for minor bleeds and 80%-100% for major hemorrhages.\textsuperscript{6} For patients with severe von Willebrand disease, both factor VIII and von Willebrand factor is often given, but other adjuncts such as intravenous or intranasal desmopressin and epsilon aminocaproic acid are also commonly administered.

Historically, cryoprecipitate and FFP were the first products used to replace coagulation factors and treat hemophilia A and B, respectively. Beginning in the 1970s, prothrombin complex concentrates (PCCs) were developed to treat hemophilia B but were also useful for replacement of other vitamin K dependent factors (II, VII, IX, and X). A relatively high risk of thrombosis dampened enthusiasm for its use.\textsuperscript{120}

Plasma-derived, specific factor concentrates were then developed as an effective therapy for hemophiliacs requiring factor VIII or IX replacement. Prior to contemporary screening methods, many patients contracted hepatitis C and HIV. However, current virucidal techniques and donor screening have minimized the risks of viral transmission from human plasma-derived products.\textsuperscript{121-3}

Recombinant clotting factors are now the most commonly used products for replacement therapy in hemophiliacs because of their efficacy and superior safety profile. Recombinant products are now recommended as first-line therapy for patients with hemophilia A and B requiring factor VIII or factor IX replacement.\textsuperscript{5,6}

Three “generations” of recombinant factor VIII (rFVIII) have been developed with continued improvement in purity and risk of infection. The first generation used human serum albumin for stabilization. The second-generation products were albumin-free and did not include the B-domain of the factor VIII gene. Third generation recombinant factor concentrates do not contain any human or animal proteins in the manufacturing process or final preparation. Multiple prospective open-label investigations have demonstrated that recombinant products are efficacious and do not cause more inhibitor formation than plasma-derived factor replacement products.\textsuperscript{12,18-24,124}

Historically, PCCs were used for factor IX replacement. Subsequently, plasma-derived factor IX concentrates were developed and found to be much less thrombogenic than PCCs.\textsuperscript{13,25-7,125-127} Over the past few decades, the purity of the factor IX concentrates has improved greatly; high purity and ultrapure products are now available. However, as with factor VIII deficiency, these have given way to recombinant factor IX (rFIX), which is just as efficacious as plasma-derived products and also eliminates any risk of infectious disease transmission.\textsuperscript{5,28-31}

**Principles Of Factor Replacement In Hemophilia**

Treatment of hemophilia revolves around using the safest product available in the quantity necessary to
effectively control the bleeding condition and minimizing further morbidity. Depending on the condition, this may range from a single infusion in the ED for mild hemarthrosis to a continuous infusion in the intensive care unit for intracranial bleeding.

Factor replacement for hemophilia is dosed on a unit per kilogram basis; 1 unit is considered to be the amount of clotting activity found in 1 mL of normal plasma. Dosing differs somewhat between factor VIII and factor IX deficiency.

- One unit/kilogram of factor VIII concentrate will increase factor VIII activity by 2%; therefore, to achieve 100% correction, 50 U/kg must be administered.6
- One unit/kilogram of factor IX concentrate will only increase factor IX activity by 1%; therefore, twice as much factor IX must be administered for the same effect: 100 U/kg are necessary to achieve 100% correction.6
- These dosing guidelines are accurate only in the absence of an inhibitor.
- The opposite relationship exists in terms of the timing of redosing between these 2 factors. Factor VIII has a half-life of 8 to 12 hours and needs to be dosed twice as frequently (about every 12 hours) as factor IX, which has a longer half-life of about 24 hours.6

Factor concentrate does not come in predefined doses; each lot will have the number of units listed on the vial. An important principle in the administration of factor concentrate is to round up the dose so as not to waste factor from a partially used vial.6

**Bypassing Agents: Treatment Of Patients With Factor Inhibitors**

Patients with hemophilia can develop inhibitory antibodies to factor replacement products, rendering these products ineffective and complicating the management of acute bleeding disorders.8,9,128,129 These IgG4 antibodies bind and inactivate circulating factor. The degree of inhibition is measured in Bethesda units, where one unit decreases factor activity by 50%. An estimated 3.6% to 17.5% of patients with hemophilia (A or B) have inhibitors.130 A population study of 3435 hemophilia patients in France found that for all patients with hemophilia A, 7% had inhibitors but for patients with severe disease, 12.8% had inhibitors.130 In the same study, inhibitors were found in 2% of all patients with hemophilia B and 4% of patients with severe disease.130 Of note, the presence of inhibitors in patients with hemophilia B may be associated with a risk of anaphylaxis.129

Multiple variables increase an individual’s likelihood of developing inhibitors, including earlier age at first exposure, use of prophylaxis, and frequency of factor use.131-135 Most patients with inhibitors should be able to provide this information (or their hematologist can), but the presence of an undiagnosed inhibitor should be suspected when patients fail to respond to routine therapy.

Until recently, the only option was to use large doses of factors VIII and IX to overwhelm inhibiting antibodies. Currently, recombinant activated factor VII (rFVIIa) (Novoseven®) and activated prothrombin complex concentrates (aPCCs) (factor eight inhibitor bypass activity [FEIBA®]) are available.136 A Cochrane Review comparing rFVIIa concentrate with aPCCs found no difference in effectiveness between the 2 products and no difference in safety as defined by tolerability and clotting complications.13,137 Two studies of the economic impact of FEIBA® versus rFVIIa use found that the cost per episode when treating acute bleeding and/or peri-operative prophylaxis was less with the use of FEIBA® than with rFVIIa.138,139

In the United States, rFVIIa is currently approved for the treatment of bleeding episodes in hemophiliacs (A or B) with inhibitors and patients with congenital factor VII deficiency. Several prospective open-label multi-center trials (study sample sizes ranging from 15 to 84 patients) have investigated the ideal dosing of rFVIIa, and a wide range of effective bolus doses were found; continuous and bolus interval dosing were found to be equivalent.140-143 See Table 7 for FDA-approved dosing recommendations.144

Several investigations of rFVIIa in patients with inhibitors in hemophilia have demonstrated that rFVIIa is effective in the treatment of intracranial and extracranial hemorrhage.145-7 Recombinant activated factor VII is also effective therapy for limb-threatening and severe abdominal bleeding in patients with inhibitors.148-50 Off-label use of rFVIIa includes treatment of patients with massive bleeding without a bleeding disorder.151 In addition, case reports suggest that patients with severe von Willebrand disease with inhibitors or refractory to standard treatment may also benefit from the use of rFVIIa.152-3

Factor eight inhibitor bypass activity®, an activated prothrombin complex concentrate, is an alternate bypassing agent for patients with hemophilia and inhibitors. Unlike rFVIIa, FEIBA® is a pooled blood product and has a small risk of disease transmission. Factor eight inhibitor bypass activity® is approved for the control of spontaneous bleeding episodes or presurgical prophylaxis in patients with hemophilia A and B and inhibitors.154 Recommended dosing ranges from 50 to 100 units/kg every 12 hours. Dosing should continue until signs of clinical improvement are achieved. Several retrospective and one open-label prospective cohort trial found that 81% to 93% of bleeding episodes achieved excellent/good hemostasis with FEIBA®.133,34,155,156 In 2010, the FDA added a black box warning for FEIBA® emphasizing the risk of thrombotic and
thromboembolic events similar to other aPCCs as discussed previously. Factor eight inhibitor bypass activity® is contraindicated for patients with a known normal coagulation (ie, a non-hemophiliac with traumatic hemorrhage), for the treatment of bleeding episodes from coagulation factor deficiencies in the absence of inhibitors, and in patients with DIC.157

Factor Replacement Products For Von Willebrand Disease
Some patients with more severe von Willebrand disease (or mild disease with more severe bleeding episodes) will require infusions of specific factor replacement products. Depending on the type of von Willebrand disease, these patients are often deficient in functioning factor VIII as well as von Willebrand factor. In contrast to patients with hemophilia, for which the products of choice are usually of high purity, concentrates containing von Willebrand factor continue to be plasma-derived. In the US, the 3 most commonly used combination products with factor VIII and von Willebrand factor are Humate-P®, Alphanate®, and Wilate®.158-160 Each product contains different concentrations of factor VIII and von Willebrand factor; therefore, dosing is calculated in the units of von Willebrand factor ristocetin cofactor (RCO) and is best determined by consulting the package insert.

Evidence supporting the use of factor VIII/von Willebrand factor concentrates consists of multiple prospective and retrospective cohort analyses, but there have been no direct comparisons of the efficacy of the 3 products currently available in the US.43,161-3 Factor VIII/von Willebrand factor replacement therapy is recommended for significant bleeding events or major surgery for patient with types 2 and 3 von Willebrand disease and patients with type 1 von Willebrand disease who are unresponsive to desmopressin.3

Adjunct Therapies
Desmopressin (DDAVP®, Stimate®, Minirin®) has been used since the late 1970s as an adjunct therapy for patients with both mild hemophilia A (ie, with some residual endogenous VIII activity) and von Willebrand disease.164 (See Table 8 on page 16.) Desmopressin, a synthetic analog of vasopressin, stimulates the release of von Willebrand factor and factor VIII from storage sites in the vascular endothelium, thus allowing many patients with minor bleeding episodes to avoid blood products and/or costly factor replacement infusions.165,166 Desmopressin is most effective for patients who have measurable levels of von Willebrand factor and factor VIII, and it can be administered via intravenous, intranasal, and subcutaneous routes.17,36,37,167,168 (Subcutaneous desmopressin is not currently available in the US.) Individual responses are quite variable, and many hematologists will conduct a desmopressin challenge to determine whether a patient with von Willebrand disease or mild hemophilia is responsive to desmopressin therapy.7,169 These results should guide ED management.

In responsive patients, desmopressin will cause a 3- to 5-fold rise in factor levels, peaking at 30 to 60 minutes for intravenous infusions and 90 to 120 minutes for intranasal administration. The plasma half-life is 5 to 8 hours for stimulating the release of factor VIII and 8 to 10 hours for von Willebrand factor.165 A common mistake is to substitute DDAVP® nasal spray for Stimate® nasal spray (both are desmopressin products), but the products have different concentrations and are not interchangeable. Stimate® is administered by intranasal spray (150 mcg intranasally for patients < 50 kg, 300 mcg for patients > 50 kg). Intravenous desmopressin is dosed at 0.3 mcg/kg intravenously over 30 minutes. Patients often experience tachyphylaxis from repeated dosing within short time intervals.38 Adverse effects include tachycardia, flushing, cramping, headache, nausea, vomiting, and a risk of significant hyponatremia if

<table>
<thead>
<tr>
<th>Bypassing Agent</th>
<th>Type Of Hemorrhage</th>
<th>Initial Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant activated factor VII (rFVIIa)</td>
<td>Mild/moderate bleed</td>
<td>90 mcg/kg every 2 hours</td>
<td>Until hemostasis achieved or response judged to be inadequate144</td>
</tr>
<tr>
<td></td>
<td>Severe bleed</td>
<td>90 mcg/kg every 2 hours</td>
<td>Continue dosing at 3 to 6 hour intervals after hemostasis achieved to maintain the hemostatic plug</td>
</tr>
<tr>
<td>Factor eight inhibitor bypass activity (FEIBA®)</td>
<td>Joint</td>
<td>50 units/kg every 12 hrs</td>
<td>May increase to 100 units/kg/dose</td>
</tr>
<tr>
<td></td>
<td>Mucous membrane</td>
<td>50 units/kg every 6 hrs</td>
<td>May increase to 100 units/kg as needed (max 200 units/kg/day)</td>
</tr>
<tr>
<td></td>
<td>Soft tissue (severe)</td>
<td>100 units/kg every 12 hrs</td>
<td>Maximum 200 units/kg/day</td>
</tr>
<tr>
<td></td>
<td>Central nervous system</td>
<td>100 units/kg every 12 hrs</td>
<td>May increase to every 6 hours dosing interval</td>
</tr>
</tbody>
</table>
Clinical Pathway: Emergency Department Management Of Immune Thrombocytopenia

**Immune thrombocytopenia**

**Thrombocytopenia without evidence of moderate/severe hemorrhage**

**ED management of stable patient with immune thrombocytopenia**

Platelets > 20-30,000/mL and asymptomatic or minor purpura only

Discharge home with close follow-up and observation

**Thrombocytopenia with life- or organ-threatening hemorrhage**

**ED management of unstable patient with immune thrombocytopenia**

Platelets < 20,000/mL and mucous membrane bleeding or < 10,000/mL and minor purpura

Strongly consider admission (Class III) for monitoring of symptoms and side effects [at least 8 hours for Rho(D)]

Choose one of the following therapies

- **Intravenous immunoglobulin (Class II)** 0.8-1g/kg IV
- **If Rh+, intravenous Rho(D) (Class II)** 50-75 mcg/kg x 1
- **Prednisone (Class II)** 1-2 mg/kg/day by mouth x 14 days or 4 mg/kg/day by mouth x 3 days
- **Emergent splenectomy (Class III)**
- **Platelet transfusions (Class III) 2 to 3 times usual amount**
- **Give intravenous immunoglobulin, methylprednisolone, or Rho(D) concurrently (Class II-III)**

Bleeding not controlled

Bleeding controlled

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient’s individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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Clinical Pathway: Emergency Department Management Of Hemophilia

Hemophilia*

No inhibitors

Suspected hemorrhage: CNS, abdominal/GI tract, compartment syndrome, ocular trauma or unstable vital signs?

YES

ED management of unstable patient

Suspected Hemarthrosis

Factor replacement to 100% physiological level before imaging

Hemophilia A

rFVIII (Class II) 50 IU/kg

Diagnostic imaging and consider admission to intensive care unit.

Hemophilia B

rFVIII (Class II) 100-150 IU/kg***

NO

ED management of stable patient

Minor bleeding: renal, oral, nasal, intramuscular (except iliopsoas), or lacerations

Factor replacement to 100% physiological level

Hemophilia A

rFVIII (Class II) 25 IU/kg

Hemophilia B

rFIX or high purity FIX (Class II) 50-75 IU/kg***

Suspected Hemarthrosis

Factor replacement to 50% physiological level

Hemophilia A

rFVIII (Class II) 25 IU/kg

Hemophilia B

rFIX or high purity FIX (Class II) 50-75 IU/kg***

Bleeding controlled?

NO

Actions to consider:
• Replace factor to 100%
• Desmopressin (Class II) if pre-tested
• Amicar® (Class III)
• Admission if bleeding uncontrolled

YES

Discharge with close follow-up with hematologist.

Known inhibitors

See Clinical Pathway on page 14.

*These actions should be taken in consultation with a hematologist.

**For pediatric patients. For adults, factor replacement is to 50%.

***Consult package insert for product-specific dosing.

See page 12 for Class of Evidence definitions.

Abbreviations: CNS, central nervous system; GI, gastrointestinal.
Clinical Pathway: Emergency Department Management Of Hemophilia With Inhibitors

Hemophilia with inhibitors

Mild bleeding**

- Inhibitor level < 5 BU/mL***
  - Low responder***
    - High dose rFVIII (Class III) or FEIBA® (Class III) or rFVIIa (Class III)
      - Bleeding well controlled?
        - YES: Discharge home with close follow-up with hematologist
        - NO: Admit for further management

Severe life- or limb-threatening bleeding

- Inhibitor level > 5 BU/mL***
  - High responder***
    - High dose rFVIII (Class III) or FEIBA® (Class III) or rFVIIa (Class III)
  - Inhibitor level > 5 BU/mL***
    - Unconfirmed but suspected inhibitors
      - FEIBA® (Class III) or rFVIIa (Class III) or plasmapheresis and rFVIII (Class III)

- Inhibitor level > 5 BU/mL***
  - Unconfirmed but suspected inhibitors
    - FEIBA® (Class III) or rFVIIa (Class III) or plasmapheresis and rFVIII (Class III)

*These actions should be taken in consultation with a hematologist. Consider inhibitors in patients who do not respond as expected to traditional factor replacement.

**For patients with mild Hemophilia A and mild bleeding. DDAVP® may be a useful first-line therapy.

***Low responders are patients with inhibitor levels < 5 BU/ml and do not develop an amnestic response following exposure to FVIII.

See page 12 for Class of Evidence definitions.

Abbreviation: BU, bethesda unit.
Clinical Pathway: Emergency Department Management Of Von Willebrand Disease

Von Willebrand disease*

History and physical and initial stabilization

Type 2B, 2N, or 3 von Willebrand disease?

YES

FVIII concentrate rich in von Willebrand factor** (Class II)

YES

Major life- or organ-threatening bleeding?

Cryoprecipitate (Class III)****

Major life- or organ-threatening bleeding?

YES

Admit to intensive care unit.

NO

FVIII concentrate rich in von Willebrand factor** (Class II)

NO

NO

Bleeding controlled?

YES

Bleeding well controlled

Adjunct therapies***

Amicar® (Class III)
Topical thrombin (Class III)

NO

Bleeding not controlled

Discharge home with close follow-up with hematologist

Admission
Consider: FVIII with von Willebrand factor infusion

*These actions should be taken in consultation with a hematologist.

**Use home supply if possible; use entire vial. Examples of FVIII concentrate with von Willebrand factor are Humate P®, Koate DVA®, Alphanate SDB®, and Wilate®. See package inserts for product specific dosing.

***Adjunct therapies may be administered at same time as replacement products or desmopressin.

****Amount of von Willebrand factor and FVIII in cryoprecipitate is variable (at least 80 IU/bag of FVIII). Dosing is based on FVIII component. See page 12 for Class of Evidence definitions.
subsequent water intake is not carefully monitored (particularly in younger children).\textsuperscript{170,171}

Anti-fibrinolytic therapies such as epsilon-aminocaproic acid (EACA)—Amicar\textsuperscript{®}—are often used as adjuncts to factor replacement in both hemophilia and von Willebrand disease. This agent inhibits plasminogen and has antiplasmin activity, aiding in initial hemostasis and preventing rebleeding, particularly orally, where enzymatic activity produces an inherently fibrinolytic environment.\textsuperscript{172} Amicar\textsuperscript{®} can be dosed as follows: loading dose 100 to 200 mg/kg (maximum 10 grams) followed by a maintenance dose of 50 to 100 mg/kg (maximum 5 grams) orally every 6 hours.\textsuperscript{173}

Epsilon-aminocaproic acid has been studied extensively for perioperative use in patients without bleeding disorders and to a lesser extent in patients with bleeding disorders.\textsuperscript{174,175} Two case series determined that EACA may be useful in patients with hemophilia with inhibitors and may have an anti-inhibitor effect separate from its anti-fibrinolytic action.\textsuperscript{176,177}

In addition, topical thrombin or fibrin glue is often used concomitantly for local control.\textsuperscript{6} The evidence supporting their use is also based primarily on case series.\textsuperscript{178-180}

**Emergent Therapy For Immune Thrombocytopenia**

The vast majority of patients with isolated, severe thrombocytopenia suffer from ITP. Unlike oncology patients where transfusions compensate for profoundly inhibited platelet production, therapy for ITP is focused on interrupting ongoing platelet destruction by the reticuloendothelial system, as noted earlier in this review.

The primary goal of therapy is not simply to increase the platelet count; rather, the specific purpose of medical intervention is to prevent bleeding complications. Therefore, decision thresholds for intervention depend on these risks. A 2010 International Consensus Report published in the journal *Blood* recommends that management of pediatric patients with ITP be based on the severity of their symptoms.\textsuperscript{110} (See Table 8.) However, specific criteria are largely based on expert consensus. Most authorities recommend instituting therapy for a platelet count below 10,000 to 20,000/mm\textsuperscript{3}. The risk of clinically significant bleeding, such as ICH, is low with platelet counts above 10,000 to 20,000/mm\textsuperscript{3} but is obviously devastating when it occurs.

The 3 standard therapies for the treatment of ITP are glucocorticoids, intravenous immune globulin (IVIG), and Rho(D) immune globulin [Rho(D)], each with different safety and efficacy profiles which are discussed in detail below. Most patients with severely depressed platelet counts will be hospitalized for initiation of therapy.

**Glucocorticoids**

Historically, low dose oral steroids served as first-line therapy for ITP. Glucocorticoids have the advantage of lower cost and excellent safety profile when compared to other therapies. However, in recent years, with the advent of IVIG and Rho(D), many hematologists deem glucocorticoids to be a second-line therapy. Prednisone (1-2 mg/kg/day) was continued until the platelet count recovered (but not necessarily normalized). Multiple investigators conducting unblinded, randomized clinical trials have determined that glucocorticoids are more efficacious than placebo in improving platelet counts during the first week of therapy.\textsuperscript{181-187} For patients with life-threatening bleeding and platelets less than 50,000/mm\textsuperscript{3}, high dose oral prednisone (4-8 mg/kg/day) or intravenous methylprednisolone 10 to 30 mg/kg/day should be administered.\textsuperscript{188}

Steroids should never be started unless the diagnosis is unequivocal (and this diagnosis should probably be made by a hematologist). Any features that are inconsistent with this diagnosis, such as hepatosplenomegaly (more than one affected cell line) or the presence of systemic symptoms such as fever, necessitate a bone marrow biopsy prior to the introduction of steroids. The risk of introducing steroids in patients with an equivocal diagnosis is masking and delaying diagnosis of malignancy. Adverse effects of systemic glucocorticoids are not benign and include hypertension, behavioral abnormalities, and hyperglycemia.\textsuperscript{172}

**Intravenous Immune Globulin**

It is believed that IVIG works by flooding Fc receptors on macrophages in the reticuloendothelial system, eliminating their ability to secure and destroy opsonized platelets. Intravenous immunoglobulin is

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Initial Dose</th>
<th>Infusion Time</th>
<th>Peak Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous desmopressin</td>
<td>0.3 mcg/kg</td>
<td>30 min</td>
<td>30-60 minutes</td>
</tr>
<tr>
<td>Intranasal Stimate® (150 mcg/spray)</td>
<td>1 spray if weight &lt; 50 kg 2 sprays if weight &gt; 50 kg</td>
<td>N/A</td>
<td>90-120 minutes</td>
</tr>
<tr>
<td>Oral Amicar® (epsilon-aminocaproic acid)</td>
<td>100 to 200 mg/kg (max 10 g/dose or 30 g/day)</td>
<td>N/A</td>
<td>45-99 minutes</td>
</tr>
</tbody>
</table>
Rho(D) Immune Globulin
Rho(D) immune globulin (WinRho® SDF) acts by coating Rh-positive red blood cells, which then provide competitive interference of reticuloendothelial Fc receptors, inhibiting platelet sequestration. (There is a predictable 1 to 2 g/dL decline in hemoglobin levels over the subsequent 2 weeks). Therefore, Rho(D) is only useful in Rh-positive patients who have not undergone splenectomy. Recommended dose of intravenous Rho(D) is 50 to 75 mcg/kg for a single dose.2

Case series and randomized controlled trials have both suggested that intravenous Rho(D) is as effective as IVIG in increasing platelet counts in patients with ITP. However, these same studies found that Rho(D) may cause more significant adverse effects. Rho(D) may produce fever, profound chills, and acute intravascular hemolysis. Similarly to IVIG, minor adverse effects of Rho(D) can be minimized with pre-medication with acetaminophen and diphenhydramine. Post-licensure surveillance has identified cases of hemolysis resulting in profound anemia requiring transfusions and hemoglobinuria with renal failure and death. Although these were rare occurrences (1.5% estimated incidence rate), the severity of the events led the FDA to add a black box warning to WinRho SDF® in 2010. Patients receiving Rho(D) must be closely monitored for at least 8 hours after administration, effectively eliminating this as a therapeutic option in the ED.

Platelet Transfusions
Rarely, patients with ITP may require intervention to immediately address active hemorrhage. Prevalently mentioned therapies merely halt ongoing destruction and rely on the bone marrow to replace increase platelet levels. With clinically significant bleeding (eg, ICH), functional platelets must be...
provided immediately, with doses as high as 2 to 3 times normal required to achieve a goal of 100,000/mm$^3$.$^{2,5,4,201,202}$ Due to ongoing platelet destruction, repeated platelet boluses (or even continuous therapy) may be required until bleeding is controlled. A recent international consensus guideline also recommends concurrently administering intravenous methylprednisolone (30 mg/kg; maximum 1 g) and IVIG (0.8-1 g/kg).$^{10,203}$

**Emergent Splenectomy**

Splenectomy is a therapy of last resort for ITP and is rarely performed emergently.$^5$ Multiple case reports have demonstrated successful treatment of refractory hemorrhage with emergency splenectomy, but no controlled trials have been conducted.$^{204-209}$ Although an effective method of increasing platelet counts, splenectomy has many potentially serious complications, including hemorrhage, infection, thrombosis, prolonged hospitalizations and death.$^{209}$

### Cost-Effective Strategies

1. **Routine labs, such as factor levels or a PT/PTT, in patients with a known coagulopathy are generally unnecessary.** Most patients with congenital bleeding disorders who present to the ED are already diagnosed. Laboratory evaluation simply documents what is already known and consumes unnecessary time and resources. Unless requested by the hematologist, laboratory studies prior to providing factor concentrate is generally unnecessary.

2. **Factor II levels and a bleeding time are not appropriate testing in the ED.** There are a plethora of tests that can be ordered in patients with a suspected but undiagnosed bleeding condition. Beyond the basic screening tests listed above, targeted testing is best left to the hematologist. Tests for suspected bleeding conditions, even one as common as von Willebrand disease, can be difficult to interpret and are best left to the specialist. Simply ordering tests “to be helpful and get things started” do not improve the timeliness, accuracy, or efficiency of the evaluation.

3. **Diagnostic radiographs provide no significant clinical information in hemophiliacs without a history of trauma.** Spontaneous hemarthroses are exceedingly common in patients with severe hemophilia (most hemophiliacs) and x-rays merely document chronic changes and acute effusions, neither of which aid in the clinical management.

4. **Ordering a type and cross where a type and screen should be sufficient.** It is common to reflexively order a type and cross when patients present with a bleeding condition. It is much more expensive than a type and screen and frequently unnecessary. Avoid ordering a type and cross unless transfusion is a likely intervention.

5. **Use the patient’s own medications when possible.** Most patients have a supply of their condition-specific factor and will bring it to the ED. Using this factor will reduce errors and will minimize the theoretical risk of increasing inhibitors with changes in brands of factor.

6. **Consider outpatient observation for patients with low but not dangerous platelet levels in ITP.** Bleeding risk is threshold related. All patients with ITP do not need admission, only those at significant risk of life-threatening complications in need of immediate therapy. These patients will require prompt (1-3 day) follow-up with a hematologist.

7. **Attempt to use adjunct therapy where appropriate before moving on to factor concentrate.** Patients with minor bleeding (oral lesions, epistaxis) and mild hemophilia A or von Willebrand disease may benefit from adjuncts such as Amicar® or desmopressin without the need for expensive factor concentrate.
Disposition

Hemophilia And Von Willebrand Disease

All patients with a bleeding disorder and clinically significant or uncontrolled hemorrhage require admission. Patients with hemophilia or von Willebrand disease and central nervous system bleeding (intracranial or intraspinal), neck injury (tracheal hemorrhage, retropharyngeal hemorrhage), gastrointestinal or intra-abdominal hemorrhage, suspected compartment syndrome, nerve compression, ocular trauma (hyphema or vitreous hemorrhage), or severe epistaxis requiring packing and ENT consultation must be admitted for either continuous or repeated dosing of factor replacement and monitoring.

The factor replacement goal in all hemophiliacs with these diagnoses is 100% (not to drop below 50%). As stated previously, the half-lives of rF-VIII and rFIX are 8 to 12 hours and 18 to 24 hours, respectively. Patients with von Willebrand disease who have these types of hemorrhages will also require admission for repetitive dosing of desmopressin and/or von Willebrand factor/FVIII replacements. Some experts recommend that activity levels for von Willebrand factor/RCo and FVIII must be monitored closely with an initial target of 100 IU/dL and a trough above 50 IU/dL for at least 7-10 days; however, other hematologists will follow the clinical response of the patient instead.

In consultation with the hematologist, patients with hemophilia or von Willebrand disease who have well-controlled, non-life threatening hemorrhage usually can be discharged with plans for close follow-up. Conditions that are often managed on an outpatient basis include epistaxis, bleeding from the oral mucosa, small intramuscular hematomas, and hemarthroses. Some of these patients may require repeat factor administration on an outpatient basis.

Immune Thrombocytopenia

Hospital admission is generally reserved for patients at risk of clinically significant bleeding. All patients with severe, life-threatening bleeding must be admitted to an intensive care setting. Patients with platelet counts of < 20,000/mm³ and mucous membrane bleeding or patients with platelet counts of less than < 10,000/mm³ and minor purpura require medical therapy with IVIG, Rho(D), or steroids and are usually admitted for parental medication administration and monitoring.

Discharged patients should have reliable families who have received teaching regarding signs and symptoms of bleeding and a physician available to give advice at all times. They must be instructed regarding the avoidance of non-steroidal anti-inflammatory drugs, and the children may not participate in contact sports or high impact activities. In general, patients with platelet counts > 30,000/mm³ who are asymptomatic or have only minor purpura can be safely discharged and may not require any treatment other than repeated laboratory monitoring.

Summary

Children with bleeding disorders frequently present to the ED with a wide variety of complaints ranging from minor to life threatening. Much of the morbidity and mortality associated with bleeding disorders can be prevented by early and aggressive recognition and intervention. Critical interventions should be initiated based on the history alone, prior to the advent of physical examination abnormalities and prior to obtaining diagnostic studies. With knowledge of the basic evidenced-based principles of emergency management outlined in this article, the emergency clinician will be able to successfully identify and intervene in the emergent presentations of bleeding disorders.

Case Conclusions

You do a quick literature search of von Willebrand disease and realize that this patient has a severe type of von Willebrand disease that has no circulating von Willebrand factor and almost no FVIII. Therefore, her epistaxis will not likely respond to desmopressin (the most commonly used therapy in von Willebrand disease). In consultation with a hematologist, you administer a Humate-P® infusion along with the adjunct therapy of oral Amicar®. You pack the nose with gauze and have the mother hold direct pressure on the area. Approximately 30 minutes later, all bleeding has stopped. A CBC demonstrates that your patient now has mild anemia, but her tachycardia resolves with a normal saline bolus.

You again consult with the hematologist and decide to send the patient home after several hours of observation, with oral Amicar® to be taken every 6 hours and instructions to follow-up in the hematologist’s office tomorrow.

Next, you take care of the 18-month-old boy with hemophilia and scalp hematoma. While simultaneously questioning the family and doing a quick physical assessment of the patient, you determine that the patient has severe hemophilia A. He does not have any known inhibitors. Other than the scalp hematoma, he has a normal physical examination and, at this time, does not show any alteration in mental status or neurologic abnormalities.

The family does not think that the patient has a history of inhibitors, and although they do not have a primary care provider currently, they did bring a vial of his rFVIII with them to the ED. You administer 50 IU/kg of rFVIII immediately. A non-contrast CT scan of the brain demonstrates a small epidural hematoma. You consult neurosurgery and hematology and transfer the patient to the pediatric intensive care unit.

Finally, you can focus on the 4-year-old with ITP...
receiving Rho(D). You realize this patient is most likely experiencing intravascular hemolysis from the Rho(D) that is being administered. You recognize that this is a potentially severe complication of Rho(D) administration and stop the infusion immediately. Prior to the Rho(D) administration, you had sent a type and screen to the lab, but you now send a type and cross because transfusions of packed red blood cells may be necessary if hemolysis continues. You urgently notify the hematologist and administer a normal saline bolus. The patient is transferred to the pediatric intensive care unit for close monitoring of clinical status, hemolytic anemia, and renal function.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available.


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3. According to this article, severe vitamin K deficiency may lead to which of the following:
a. Hemorrhagic disease of the newborn
b. Bone loss
c. Vision loss
d. Low birth weight

4. Emergency clinicians should always use the hospital’s supply of a therapeutic agent instead of one the patient brought from home.
a. True
b. False

5. Patients with bleeding disorders may present with which of the following complaints:
a. Abdominal or flank pain
b. Muscle pain
c. Headache without trauma
d. All of the above

6. Which of the following statements are true with regards to low-dose oral steroids as therapy for immune thrombocytopenia?
a. They have an excellent safety profile.
b. They cost more than other therapies.
c. With the advent of IVIG and Rho(D), they are now considered second-line therapies by many hematologists.
d. Both A and C

7. All patients with a bleeding disorder and clinically significant or uncontrolled hemorrhage require admission.
a. True
b. False
Carbon monoxide (CO) is an odorless, colorless gas released from the incomplete combustion of burning hydrocarbons. CO has been called a “great imitator” and “silent killer.” CO poisoning is the most common preventable toxic exposure resulting in death in children 12 years and younger. In this age group, it is typically an accidental poisoning. In adolescents, especially males, CO poisoning may be intentional. It has also been described as a form of child abuse by caregivers. Finally, there has been some evidence that there is a link between CO poisoning and sudden unexpected infant death syndrome (SUIDs); however, one study retrospectively reported no association in a series of 50 infants who died unexpectedly.

Further evaluation is necessary to elucidate a link between SUIDs and CO poisoning. CO poisoning is frequently associated with inhalation injuries. When associated with a thermal burn, it is easier to recognize a carbon monoxide exposure. However, CO poisoning may go unrecognized and undetected leading to morbidity and mortality. Patients with CO poisoning often present to the emergency department with a constellation of non-specific symptoms. Furthermore, CO poisoning is not detectable on routine drug screens. The clinician must pay close attention to the details of the history and have a low index of suspicion in order to avoid missing this potentially lethal exposure.

This issue of Pediatric Emergency Medicine Practice is an evidence-based review of the diagnosis and management of patients with CO poisoning.

**Physician CME Information**

**Date of Original Release:** August 1, 2011. Date of most recent review: July 10, 2010.

**Termination date:** August 1, 2014.

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**Needs Assessment:** The need for this educational activity was determined by a survey of the editorial board, including the editorial review board of this publication and review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP, and evaluation of prior activities for emergency physicians.

**Target Audience:** This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

**Goals:** Upon reading Pediatric Emergency Medicine Practice, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

**Objectives:** Upon completion of this article, you should be able to: (1) communicate intelligently with the hematology consultant about patients with hematological conditions in the ED; (2) manage common bleeding complications in patients with hemophilia; (3) be familiar with various factor concentrate products and their use; (4) identify and begin the appropriate evaluation for suspected, previously undiagnosed bleeding conditions, including immune thrombocytopenic purpura; and (5) recognize less common conditions associated with coagulopathy.

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