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Part I of this two-part series outlined platelet-related disorders that could lead to hemorrhagic emergencies. A number of other conditions, including hemoglobinopathies and other inherited disorders, can produce a wide range of symptoms. Transfusion reactions also must be recognized by the emergency physician and managed promptly.

With these issues in focus, the final part of this two-part series presents a strategy for diagnosing inherited blood disorders and managing them in the acute care setting.

— The Editor

Hematologic Emergencies and Life-Threatening Bleeding Disorders: Differential Diagnosis, Evaluation, and Management

Part II: Hemophilia, Sickle Cell Anemia, and Transfusion Reactions

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Hereditary Disorders of Coagulation: Hemophilia

Hemophilia is a coagulation disorder primarily caused by a deficiency in one of two circulating plasma proteins. Hemophilia A, or "classic" hemophilia, is caused by a deficiency of factor VIII and is the most common cause of hemophilia in the United States. Hemophilia B, or Christmas disease, is caused by a deficiency of factor IX. Together, these forms of hemophilia make up about 99% of all cases of hemophilia patients, with the remaining 1% composed of individuals with rarer forms of factor deficiencies. Hemophilia A and B are clinically indistinguishable from each other and specific factor testing must be done to clarify which form an individual has.

Both hemophilia A and B are X-linked recessive disorders. Hemophilia most commonly is seen in men, and women are asymptomatic carriers. Interestingly, approximately one-third of new cases of hemophilia A and one-fifth of new cases in hemophilia B arise from a spontaneous gene mutation.

Bleeding manifestations in patients with hemophilia are directly attributable to the decreased plasma levels of either factor VIII or IX. Patients with factor levels of 5-30% of normal are classified as having mild disease; these patients usually will bleed only after trauma. Patients with levels of 1-5% of normal factor levels are classified as having moderate disease; they may bleed spontaneously, but their bleeding still most commonly is related to a traumatic event. Individuals with factor levels below 1% are classified as having severe disease, and will experience spontaneous bleeding episodes.

Treatment of patients with hemophilia relies on either the replacement of missing factors or, for those who have mild factor VIII deficiency, stimulating the body to secrete additional clotting factor from intracellular stores.[1]

Clinical Manifestations. Depending on the severity of the disease, both forms are characterized by easy bruising and recurrent bleeding into the joints and muscles. While the joints and muscles are the most common areas into which bleeding occurs, hemorrhage also may occur in the abdomen, retroperitoneum, or central nervous system. Any trauma or surgical procedure may result in prolonged and difficult to control bleeding.

While adults often know they have hemophilia, young children may not have been diagnosed before they present to the emergency department (ED). A family history may reveal bleeding disorders; however, because spontaneous mutations do occur, there may not be a prior family history. Therefore, hemophilia should be suspected in any young child who presents to the ED with excessive bruising or significant bleeding in the joints, muscles, or central nervous system that is spontaneous or out of proportion to the history of trauma. Depending on the severity of the disease, prior bleeding episodes may have occurred only after a surgical procedure, such as a tonsillectomy, or may be a new problem for a menstruating adolescent. A medication review also should be completed to determine if the bleeding may be related to a new medication. While excessive bruising and bleeding can lead to an eventual diagnosis of hemophilia, a more common and tragic cause to consider is child abuse.

Laboratory Testing. A complete blood count (CBC) with platelets, along with a prothrombin time (PT) and an activated partial thromboplastin time (aPTT), should be ordered in those patients in whom a bleeding disorder is suspected. In patients with hemophilia, the CBC and PT, which measures the extrinsic coagulation cascade, will be normal, while the aPTT, which measures the intrinsic coagulation cascade, will be abnormal. Bleeding time in both hemophilia A and B will be normal. Assays can be done to help determine the exact nature of the clotting deficiency if the diagnosis is new. Coagulation studies are not always necessary if the patient carries a known diagnosis.

Initial Assessment. In the known hemophiliac, the physician must decide whether clotting factor replacement is necessary. Patients with obvious bleeding will require immediate factor replacement, but other cases can be more subtle. Simple injuries, such as ankle and cervical sprains, all can be complicated by delayed bleeding and generally will require therapy. By initiating treatment at the first onset of symptoms, it is possible to limit bleeding and local tissue damage. Infants with hemophilia are difficult to evaluate. Again, if an infant is irritable and no other source is found, there should be a presumption of occult bleeding. Those patients undergoing invasive procedures also will require factor replacement. Many patients and their families will have a thorough understanding of their disease and will know to seek treatment at the first sign of problems. Thus, there may be little outward evidence of disease, but the patient may know something is wrong.

Treatment. *Principles of Replacement Therapy.* Genetically engineered recombinant factors VIII and IX were developed in the mid-1990s. These factors dramatically decreased the risk of viral transmission. Along with the development of these recombinant factors, technology also improved the purification of other plasma-derived replacement factors. Thus, there are now two different treatment options: recombinant factor replacement; and plasma derived, purified factor replacement. The highest level of purity comes from the recombinantly produced factors. However, the new techniques in purification have significantly improved the quality of plasma-derived factors. Nevertheless, variability in purity does exist among the different products and it does remain possible for even the treated plasma-derived products to potentially transmit viruses such as hepatitis A and parvovirus.[2] Interestingly, the recombinant factors contain human albumen and, therefore, the recombinant products are not necessarily safer than the monoclonally purified plasma factors. No difference in safety has been established. Most pediatric patients are treated with either monoclonal antibody-purified plasma-derived factors or recombinant factors. Little distinction is made because both are high-quality, safe products. Donated cryoprecipitate also may be used when available.

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Table 1. Factor Replacement Guidelines

SITE	MINIMUM FACTOR LEVEL	HEMOPHILIA A DOSE	HEMOPHILIA B DOSE	ADDITIONAL INFORMATION
Muscle	40-50%	20-40 U/kg	40-60 U/kg	Admit, monitor total blood loss, watch for compartment syndrome.
Joint	30-50%	20-40 U/kg	30-40 U/kg	Orthopedic consult for splinting and physical therapy.
Epistaxis	Initially 80-100%	40-50 U/kg	80-100 U/kg	Typical local measures should be used.
Oral mucosa	Initially 50%	25 U/kg	50 U/kg	Local measures and antifibrinolytic therapy will decrease need for additional factor replacement.
GI bleeding	Initially 100%	40-50 U/kg	80-100 U/kg	Consultation with GI is appropriate to identify a lesion.
Central nervous system	Initially 100%	50 U/kg	100 U/kg	Neurosurgical consultation should be early. Lumbar puncture on these patients requires factor replacement.
Trauma	Initially 100%	50 U/kg	100 U/kg	

While advances in technology have increased safety in the treatment of the hemophiliac patient, these new products are expensive. In the case of hemophilia B, low purity agents are less costly but have potential for viral transmission. They often contain not only factor IX, but also significant amounts of factors VII, X, and prothrombin. Prolonged use of the less pure concentrates may increase the risk of disseminated intravascular coagulation, or in some cases, cause paradoxical clotting. For this reason, despite increased cost, most patients receive more purified factor IX preparations. There is a factor IX preparation that is entirely free of all human blood products.

The dosing regimen used in the hemophilic patient is based on the clotting factor's volume of distribution, the half-life of the factor, and the hemostatic level of factor required to control the bleeding. Clotting factor is dosed in "units" of activity. One unit of factor represents the amount of factor present in 1 cc of normal plasma. In the case of hemophilia A, one unit of factor VIII raises the plasma level by approximately 0.02 U/mL (2%). The half-life is approximately 12 hours. For hemophilia B, one unit of factor IX will raise the plasma level by approximately 0.01 U/mL (1%). The half-life is approximately 18-24 hours. Calculation of the amount of factor needed can be based upon body weight and plasma volume, but an easier formula is based upon the amount that one unit of factor raises the factor level. These calculations can be made as noted:

- Factor VIII required = weight in kg $\times$ 0.5 $\times$ % change in factor activity needed;
- Factor IX required = weight in kg $\times$ 1.0 $\times$ % change in factor activity needed.

When less severe bleeding occurs in soft tissue, muscle, or joints, the appropriate factor replacement level is 30-50%. Usually, three doses are sufficient to control bleeding and prevent additional bleeding.

When major bleeding occurs in the central nervous system, gastrointestinal tract, neck, throat, or large muscle, or when a severe injury is present, factor replacement levels between 80% and 100% are necessary. In these cases, therapy will need to continue for days or weeks. Factor replacement can be given as bolus therapy or as a continuous therapy. Continuous therapy may help decrease the total amount of factor required.[3] Management of different types of bleeding is listed in Table 1. Patients with significant bleeding will require transfer to a center with experience treating these patients. Most severe bleeding episodes presenting to the ED will require factor levels to approach 100%. The emergency medicine physician should attempt to accomplish this while trying to arrange for transfer or admission with the hematologist.

There may be rare instances when a child presents with what appears to be a previously undiagnosed bleeding disorder. In these cases, the use of a specific factor may not be possible and the emergency medicine physician may need to use fresh frozen plasma (FFP) to control bleeding until definitive studies can be completed. As is true of the other replacement factors, the measures used to purify FFP have improved and the risk of transmitting diseases such as human immunodeficiency virus (HIV) and hepatitis is minimal. FFP contains all of the plasma clotting factors, with an average concentration of 1 unit/mL. However, the actual concentration of each unit may vary. To optimize use of FFP, consultation with a hematologist would be helpful.

Specific Cases. *Oral and Mucosal Bleeding.* Bleeding from the mouth is common in hemophiliacs, particularly in children with hemophilia. The fibrinolysins in saliva worsen this bleeding. When faced with oral bleeding, the physician should identify the bleeding site, clean the area of inadequate clot, and cover it with dry topical thrombin. Initial factor replacement should be 70-100%. Additional therapy may still be needed to prevent bleeding when clotting does not occur. When treating oral or mucosal bleeding, antifibrinolytic agents (e.g., epsilon-aminocaproic acid [Amicar]) are available as adjunctive therapy to factor replacement. For very superficial mucosal injuries, antifibrinolytic therapy alone may be sufficient. The dose of epsilon-aminocaproic acid is 75-100 mg/kg for children every six hours, and 6 gm every six hours for adults. This medication is available in oral and IV forms. Topical hemostatic agents used to help control oral or nasal bleeding include microfibrillar collagen hemostats, thrombin, and absorbable gelatin sponges. Since few emergency medicine physicians will have significant experience with these agents, consultation is advised.

Mild Hemophilia A. Patients with mild hemophilia A (factor levels of 5% or greater) who have mild bleeding may not require factor replacement in every case;[1] rather, these patients may be given desmopressin (DDAVP). When giving intravenous DDAVP, the dose is 0.3 ug/kg over 30 minutes. Stimate is the

Table 2. Laboratory Tests and Abnormalities Associated with von Willebrand's Disease

TESTS:
Bleeding time
Activated partial thromboplastin time (aPTT)
Factor VIII coagulant activity
vWF antigen
vWF activity
COMMON ABNORMALITIES:
Prolonged bleeding time
Low or normal vWF antigen
Low vWF activity
Factor VIII activity may be variable
aPTT activity may be variable

only intranasal form of DDAVP that is concentrated enough to be an option for use in hemophilia. If this medication is used, it is important to remember that it is a potent antidiuretic agent and that fluid restriction will be necessary during and after its use.

For children older than age 5, a single spray in a single nostril is adequate. For adolescents and adults, a single spray should be administered in each nostril. These treatments will increase the factor VIII level by 2-3 times. This treatment can be repeated, but the patient's stores of factor VIII will be depleted and subsequent effects will be lessened.

Inhibitors. Unfortunately, some people will develop inhibitors in response to the clotting factors used to treat their bleeding episodes. These inhibitors not only interfere with the effectiveness of factor replacement therapy, but also have been reported to cause anaphylaxis in patients with hemophilia B.[4] Inhibitors occur in 20-25% of those with hemophilia A,[1] and in 1-2% of those with hemophilia B.[4,5] These patients are more difficult to treat, but options do exist. When inhibitors are present, these patients can receive high-dose factor VIII concentrates, prothrombin complex concentrates, recombinant factor VIIa, or porcine factor VIII. Given the complexity of these patients, consultation or transfer to a center with hematology is recommended.

Hereditary Disorders of Coagulation: Von Willebrand's Disease

Von Willebrand's disease (vWD) is the most common congenital bleeding disorder; it is present in 1% of the population.[6] Knowledge of the function, structure, and synthesis of von Willebrand's factor (vWF) has increased recently. It is now understood that this disease is a group of disorders caused by different abnormalities of vWF. The disease is heterogeneously inherited and expressed. Although there are multiple subtypes, these can be classified into three major groups. Type I is the most common and is a partial quantitative disease, type II is a qualitative (abnormal function) disease, and type III is a severe and almost complete deficiency of vWF.

In normal hemostasis, vWF serves two key roles. It is a cofactor for platelet adhesion and the carrier protein for factor VIII. Circulating vWF does not bind directly to platelets, but when exposed to the subendothelial matrix, vWF undergoes a conformational change that allows it to bind to platelet glycoprotein Ib. The interaction of vWF and platelet glycoprotein Ib leads to platelet adhesion and activation. This factor also is the carrier protein for factor VIII in the plasma. When vWF is absent, the half-life of factor VIII is decreased dramatically because vWF protects the factor VIII from proteolytic degradation in the plasma. If vWF fails to bind to factor VIII, the clinical presentation is similar to hemophilia A.

Mucosal bleeding symptoms are common in people with vWD, particularly in children and adolescents. This includes recurrent epistaxis and menorrhagia in young women. Depending on disease severity, patients may not know that they have a bleeding disorder until a surgical procedure or trauma results in severe bleeding.

Laboratory Tests. If the diagnosis has not been made previously, lab testing may be undertaken. Tests to be performed include the following: bleeding time, aPTT, factor VIII coagulant activity, vWF antigen, and vWF activity.[7] It is possible for some lab tests to be normal even in those with disease. However, the common abnormalities include: prolonged bleeding time, low or normal vWF antigen, and low vWF activity. Factor VIII activity may be variable, as can the aPTT. *(See Table 2.)*

Treatment. Management of many children with minor bleeding disorders can be accomplished by the emergency medicine physician with the aid of a hematologist. From the standpoint of the emergency medicine physician, it is important to realize that there are medications that should not be given to a child with vWD. Those medications with known antiplatelet effects should be avoided. These include aspirin and nonsteroidals, antiplatelet agents, heparin, and certain antibiotics, as well as others.

Nontransfusional Therapies. Recently, DDAVP (1-deamino-8-D-arginine vasopressin) has become a mainstay of therapy for some patients with type I vWD. For the other types of vWD, DDAVP still may work in conjunction with other therapies.[8] This medication allows for the release of vWF from storage sites within the endothelium. In responsive individuals it causes a two- to four-fold increase in vWF. DDAVP also seems to have an effect on the endothelium that promotes hemostasis.

DDAVP may be used to treat bleeding complications, as well as prepare patients for surgery or minor procedures. However, prior to its use the clinician should know whether the patient is responsive to this medication. The dose used for hemostasis is much higher than that used for the treatment of diabetes insipidus. The dose is given intravenously, and may be repeated every 12-24 hours. Subcutaneous use has been shown to be effective, and there is now a high-dose intranasal form. The intranasal form is best studied for home use in cases of injury. Tachyphylaxis occurs more often in hemophilia patients than in those with vWD, however, dosing more frequently than every 24 hours may result in this phenomenon.

Transfusional Therapies. Plasma derivatives that contain vWF have been used for those patients who do not respond to DDAVP. The chosen product needs to have vWF in the high-molecular weight form to be effective. Cryoprecipitate meets this objective (contains factor VIII and vWF), but there is concern about the potential for viral transmission. Administration of 10 bags of cryoprecipitate every 12-24 hours usually will control bleeding. Rather than using this, some clinicians prefer factor VIII products that contain vWF and have undergone viral inactivation

processes. Humate-P is an intermediate purity factor VIII concentrate that has significant amounts of vWF and can be used to treat bleeding episodes. Cryoprecipitate from a limited number of donors is another possibility. Platelet transfusions may benefit patients with certain types of vWD (type 3) who do not respond to vWF-containing concentrates of cryoprecipitate.[9]

Additional Treatments. Those patients who have a history of vWD and a significant nose bleed should receive the normal measures taken to control bleeding. If these are not successful, intranasal application of porcine strips, or porcine strips sprinkled with microfibrillar collagen (Avitene) may help control bleeding. Cauterization is necessary in some cases.

Menorrhagia is a common complaint in young women with vWD. Birth control pills can help raise vWF levels and limit the degree of menstrual bleeding.

For bleeding or planned procedures in the oral cavity, an antifibrinolytic agent should be used. Epsilon-aminocaproic acid can be taken orally. Cyclokapron can be made into a mouthwash. These may be used for 5-10 days after an injury or a surgical procedure.

Disorders of Hemoglobin Structure and Production: Sickle Cell Disease

The most commonly encountered disorders in this category include sickle cell disease and the thalassemias. However, there are several categories into which hemoglobin disorders can be placed. This includes hemoglobins that tend to gel or crystallize (sickle cell anemia), unstable hemoglobin, hemoglobin with abnormal oxygen binding properties, hemoglobin that is readily oxidized to methemoglobin, and hemoglobin chains that are synthesized at unequal rates (thalassemias). A complete discussion of all these entities is beyond the scope of this article. Therefore, the diseases that are the most likely to be encountered by the emergency medicine physician will be discussed.

Sickle Cell Anemia. Sickle cell anemia is caused by the substitution of the amino acid valine for glutamine at a specific point in the ß-hemoglobin chain. The result of this mutation is that deoxygenated hemoglobin S polymerizes and distorts the shape of the red blood cell. Sickle hemoglobin also has additional adverse effects on the red cell membrane. The ultimate effect is to decrease the half-life of the red blood cell (chronic ongoing hemolysis), causing episodic periods of vascular occlusion and resulting in tissue ischemia. Few organ systems are spared. This defect is inherited as an autosomal recessive trait. Disease is seen in those patients who are homozygous for the sickle gene (HbSS). Those people with sickle cell trait (HbAS) usually are asymptomatic, except in rare cases of severe stress. Approximately 8% of the African-American population carries the gene, and approximately 0.15% of African-American newborns are homozygous.[10] While sickle cell anemia accounts for a majority of the cases of this disease other sickle cell disorders may result from the coinheritance of a sickle cell gene and ß-thalassemia or other hemoglobin abnormality.

The ongoing pathophysiologic effects of sickle cell disease include a wide range of problems. Sickled red blood cells cause microvascular sludging and obstruction. This obstruction worsens hypoxia and causes acidosis, which causes further sickling. As stated previously, the abnormal shape of the red cells causes a decreased lifespan and yields a chronic hemolytic anemia. The combination of hemolytic anemia and recurrent vasoocclusive events give the basis for this chronic disease.

At one time patients with sickle cell disease had a significantly decreased lifespan. While the lifespan of these patients has improved, they still suffer significant complications related to their disease and the emergency medicine physician can expect to see a variety of presentations.

Clinical Presentations. Most patients who present to the ED will know that they have a history of sickle cell disease. Newborn screening commonly takes place in the United States, so parents generally know about this disease. However, sickle cell anemia should be considered in any African-American child who presents with unexplained pain or swelling in the extremities, anemia, or splenomegally. The peripheral smear can be normal; therefore, to definitively make the diagnosis, specific testing, such as hemoglobin electrophoresis, may be necessary. Specific complications of sickle cell anemia and their presentations will be discussed below.

Vasoocclusive Pain Crisis. Acute sickle crisis is a common presenting complaint to the ED. The initiating event may not be identifiable, but stressors, such as altitude, cold, dehydration, and infection, have been identified. As a result of intravascular sickling and small vessel occlusion, infarction of bone, viscera, and soft tissue occurs. This can produce pain, as well as other symptoms related to the affected organ. Initial management of these patients includes pain control, judicious hydration, and an assessment of the cause of the current crisis, as well as a search for additional complications. Adequate pain control is important in the management of these patients and should be addressed in all patients who complain of sickle cell pain. Oxygen commonly is used, but has not been proven to be of benefit. Generally, a CBC and reticulocyte count help determine the degree of anemia and insure that the marrow still is producing red cells. It is not uncommon for the sickle cell patient to have a low-grade temperature, as well as an elevated white blood cell count. This combination may make it difficult to differentiate whether an infection is present during a crisis. If the white cell count has a left shift and is elevated above 20,000 WBCs/mm^3, infection should be considered. If fever or abdominal pain is present, urine should be checked. Radiograph is appropriate for patients with significant fever, or when any pulmonary complaints are present.

While the pain crisis may resolve, there are several significant complications that may result from the episode.

Bone Pain. Bone pain is common during a sickle cell crisis and may include the back and the extremities. Commonly, there will be no physical findings. The complaint of localized pain to the hip with difficulty ambulating should raise the possibility of aseptic necrosis of the femoral head. Localized bone pain may be present, but if redness, warmth, or swelling are present this should raise the concern for infection. Bone infarctions may cause symptoms similar to osteomyelitis and additional testing and consultation may be needed to ensure infection is not present. Radiographs may show evidence of aseptic necrosis or osteomyelitis, but also may be normal even when necrosis or infection is present. Bone

Table 3. Acute Chest Syndrome in Sickle Cell Disease

ACUTE CHEST SYNDROME:
Any acute illness with a new pulmonary infiltrate found on radiograph
Onset of chest pain associated with fall in hemoglobin level from normal baseline
PRESENTING SIGNS:
Pleuritic chest pain
Fever
Cough (usually nonproductive)
Tachypnea
TREATMENT:
Closely monitor fluid status
Oxygen
Pain control
Broad-spectrum antibiotics
Transfusion or exchange transfusion (associated with improvement)

infarcts usually will not show up on radiographs. A bone scan should help differentiate infection from infarction. In young children, one of the first manifestations of sickle cell disease is dactylitis (hand-and-foot syndrome). The syndrome is thought to be due to infarction of the red marrow with associated periosteal inflammation. As the child grows, this hematopoietic tissue is replaced by fatty tissue.[11] The syndrome manifests as fever and painful swelling of the hands and/or feet. Some redness and warmth may be present. Management is symptomatic.[12]

Chest Syndrome. The acute chest syndrome may be used to describe any acute illness with a new pulmonary infiltrate found on radiograph. The patient may have pleuritic chest pain, fever, cough (usually nonproductive), and tachypnea. *(See Table 3.)* The exact etiology of the chest syndrome is unclear, but infection, infarction, and fat embolism all have been implicated.[13] However, it is not uncommon to find little evidence of infection.[14] Ultimately, it can be difficult to distinguish pneumonia from pulmonary infarction, which is why any finding on radiograph is simply referred to as acute chest syndrome. In fact, by clinical grounds alone it may be difficult to tell if a patient has pulmonary involvement at all, and one recent study recommended chest radiograph in all febrile sickle cell patients because the mortality is high if the disease is initially missed.[15] The onset of acute chest syndrome may be associated with a fall in hemoglobin level from the normal baseline. Pulmonary infiltrates may be present in one lobe or be diffuse and bilateral. Pleural effusions may be present. Severe cases may progress rapidly to respiratory failure.

A high index of suspicion should be present for any sickle cell patient presenting with fever, pleuritic chest pain, and any respiratory symptoms. The initial chest radiograph may be normal.

Treatment involves close monitoring of fluid status, oxygen, and pain control. Physicians should should assume that the cause is sickling, as well as infection. Broad spectrum antibiotics should be given. Transfusion or exchange transfusion are associated with improvement.[19,23]

Abdominal Crisis. Generalized and constant abdominal pain is not uncommon in sickle cell crisis. However, it may be difficult to distinguish between infarction of the abdominal and retroperitoneal organs associated with a sickle cell crisis, vs. a focal abdominal problem such as appendicitis. Frequently, the patient can determine that the pain is similar to prior episodes. If there is doubt, repeated abdominal exams should be done to assess for progression of pain and peritoneal signs. If the patient is severely ill, the abdominal pain should not be assumed to be secondary to a typical vasoocclusive crisis.

Hepatic infarction may cause the acute onset of jaundice and abdominal pain and can be difficult to distinguish from hepatitis or cholecystitis. It is important to consider biliary disease because cholelithiasis is seen in 30-70% of sickle cell patients.[16] Both hepatic infarction and biliary obstruction should show elevations of liver functions and bilirubin. Ultrasound may aid in the diagnosis. Management for abdominal pain crisis should include judicious fluid use and adequate pain management.

Renal System. The major problems related to acute sickle crisis in the genitourinary system include papillary necrosis and, in males, priapism. Papillary necrosis may result in hematuria, but red cell casts are uncommon. Generally this condition will respond to fluids and close monitoring of red cell levels to ensure anemia does not worsen.

Priapism may occur during a sickle cell crisis and manifests as severe, painful swelling of the penis. Initial treatment is fluid hydration and pain control. If this does not improve the symptoms, other options include aspiration of the corpora and transfusion. Exchange transfusion may work if these other modalities do not. Early involvement of urology and hematology is mandatory.

Additional Systemic Manifestations of Sickle Cell Disease.

Spleen: Splenic Infarction. The spleen is particularly susceptible to the effects of sickled cells. Over time, microinfarctions result in a spleen that is essentially nonfunctional. The Cooperative Study for Sickle Cell Disease demonstrated that the proportion of children with sickle cell disease who are functionally asplenic is 14% at age 6 months, and reaches 94% by age 5.[17] Thus, young children are at risk for sepsis from encapsulated organisms. Given this fact, immunizations and parental education are critical to minimize the risk of infection. As sickle cell patients age, their risk of overwhelming sepsis decreases, but they remain predisposed to infections.

Splenic Sequestration. Splenic sequestration is more common in children than adults, and it remains an important cause of morbidity and mortality.[18] This manifests by the sudden enlargement of the spleen, with an acute fall in the hemoglobin level due to sequestration of the blood volume within the spleen. Platelets also may be sequestered, resulting in moderate thrombocytopenia. The reticulocyte count should remain elevated. Symptoms include tachycardia, hypotension, pallor, lethargy, and abdominal fullness.[14] Left upper quadrant pain may or may not be present. The spleen should be enlarged and will be unusually hard.

Therapy includes volume resuscitation, which may mobilize some of the red cells trapped within the spleen.[14] Transfusion may be necessary. Clinicians should search for a precipitating infection. Recurrence of this syndrome is common.

Hemolytic Anemia. Patients with sickle cell disease have a chronic hemolytic process due to the shape of the red cells. With infections, the hemolytic process may worsen. Typically, reticulocytosis will increase in response to the increased red cell destruction. Acutely, the patient may notice symptoms of worsening anemia and scleral icterus. It is uncommon for the hemolysis to be so severe as to require intervention. Lab values will support the diagnosis (CBC, peripheral smear, LDH, direct bilirubin, UA). If necessary, blood transfusion may be given.

Aplastic Crisis. Aplastic crisis is more common in pediatric patients than adults.[19] Generally, the increased production of red blood cells by the bone marrow compensates for the increased rate of destruction. Aplastic crisis results in rapid decline of the hemoglobin level and reticulocytopenia. The most common cause of aplastic crisis appears to be infection, specifically parvoviris.[20] Folate deficiency and bone marrow necrosis also may play a role.[21]

These patients generally will present with increasing fatigue and pallor and no evidence of hemolysis. The hemoglobin level unusually will be low, and few or no reticulocytes will be present. Generally, this syndrome is self-limiting and the marrow will begin producing red cells spontaneously within a week. Transfusion may be required in the interim.

Neurologic Disorders. Complications include stroke and subarachnoid bleeding, as well as isolated functional loss. Strokes usually develop abruptly and with little warning, but may occur during episodes of vasoocclusive pain. In some cases, vague symptoms that are consistent with a transient ischemic attack may be present and always should be assumed to be potential warnings of impending stroke. The cause of strokes in most patients is cerebral infarction due to occlusion or narrowing of large cerebral vessels. The exact mechanism by which sickle cell disease causes endothelial damage in these large vessels is not clear. Although stokes may occur in children with sickle cell disease, the rate increases with advancing age.[22]

Supportive therapy should be initiated to address airway and vital sign abnormalities. Acute treatment is emergent simple or partial exchange transfusion.[14,19] Cerebral aneurysms also are more common in sickle cell patients, perhaps due to local vessel occlusion or ischemia. Therefore, if symptoms of stroke do not improve with transfusion, or if the history suggests that subarachnoid hemorrhage may be present, lumbar puncture should be completed if the head CT is normal. Children who suffer a stroke have a high risk of recurrence.

Disorders of Hemoglobin Structure and Production: Thalassemias

The thalassemias are a diverse group of disorders that are characterized by the defective synthesis of globin chains, which results in multiple complications. The hallmark of these disorders is a microcytic, hypochromic, hemolytic anemia. These disorders are most common in those of Mediterranean, Middle Eastern, and Southeast Asian descent. Like sickle cell disease, the abnormalities found in those with thalassemia are thought to be protective against malaria.

The normal adult red blood cell contains three forms of hemoglobin (Hb). The predominate form is HbA, which is composed of two alpha chains and two beta chains. Small amounts of HbA2 and HbF also exist in the red cell. The thalassemias are disorders characterized by an inability to produce a normal adult hemoglobin. Specifically, the ß-thalassemias have diminished production of the ß-globin chain, which allows unmatched alpha chains to accumulate. The accumulating, unmatched chain causes toxicity within the developing erythroid precursor cells (resulting in early death).[23] Those cells that are produced have decreased hemoglobin, which accounts for the hypochromia and target cell formation. Patients with α-thalassemia develop an excess of ß-globin chains. Interestingly, in the severe α-thalassemias, ineffective erythropoiesis is less problematic. Rather, increased destruction of the cells due to the structural abnormality is more prominent.

Both forms of thalassemia are characterized by differing extremes of anemia. The degree of anemia depends upon the amount of ineffective erythropoiesis and premature destruction of the circulating red blood cells. Depending on the severity of the anemia, the associated hypoxia triggers compensatory mechanisms in an attempt to increase red blood cell production. This causes enlargement of the reticuloendothelial organs and expansion of the bone marrow cavity, which leads to osteopenia. The complications of these attempts to increase red cell production are compounded by the complications that result from the chronic destruction of peripheral red blood cells.

The ß-thalassemias have three clinical syndromes: ß-thalassemia major (Cooley's anemia), ß-thalassemia minor, and thalassemia intermedia. For the α-thalassemias there are five clinically distinct syndromes, and the severity of disease will depend on the number of genes that are deleted. The most severe form of α-thalassemia occurs when there is a deletion of all of the alpha chain genes. This is called hemoglobin Bart's and infants are born hydropic. This condition is inconsistent with life. Other than this most severe form, individuals with either alpha- or beta-thalassemia can be minimally to severely affected. Several of the varieties are discussed in this issue. The diagnosis of either alpha- or beta-thalassemia should be considered in any person with very low median cell volume (MCV) median cell volume and a red cell count greater than 5 million cells/uL.

Hemoglobin H Disease. This is an α-thalassemia in which some alpha genes still are present. This form may present in the neonatal period as a severe hypochromic anemia, but these children can survive. Later in life the clinical picture includes a hypochromic, microcytic anemia with jaundice and hepatosplenomegaly. These patients may not require regular transfusions, but in conditions of increased oxidative stress (that may cause precipitation of the unstable hemoglobin H resulting in hemolysis) or infection, a transfusion may be necessary. Most of these patients will know their diagnosis and the emergency medicine physician should provide supportive care and blood transfusion when necessary. In addition, the physician also should avoid any medications that may precipitate hemolysis.

ß-Thalassemia Major (Cooley's Anemia). This disorder is characterized by a severe anemia that begins in the first year of life. Growth and weight gain may decrease; then the child develops hepatosplenomegaly, jaundice, expansion of the erythroid

marrow (causing bone changes and osteoporosis), and increased susceptibility to infection. In this case the anemia is severe and requires regular and life-long blood transfusions, which unfortunately, produce their own cumulative effect on the child.[24] The transfusions eventually cause an iron overload which, if untreated, results in cardiac hemachromatosis.

A CBC in these children shows a low MCV with microcytic and hypochromic cells. Variation in the size and shape of the red cells will be notable, as will the presence of nucleated red blood cells. This diagnosis should be considered in any child with a severe microcytic anemia and the appropriate ethnic background. For those with a known diagnosis who present to the ED with significant symptoms related to anemia or hemolysis, transfusion should be considered along with a search for precipitating events. During the transfusion, the patient should be monitored for fluid overload. Many of these patients may have had a splenectomy and this history should be sought because of the risk of infection. Chelation therapy may be addressed by the admitting hematologist.

ß-Thalassemia Minor (ß-Thalassemia Trait). Patients with this form of thalassemia are heterozygous for the beta globin mutation and have only mild, if any, anemia. Splenomegaly may be present but is not common. On their blood smear, these patients may have microcytosis and hypochromia as well as basophilic stippling. These patients generally will not have clinical manifestations of their disease and may only come to attention during an evaluation for a mild anemia.

Complications of Blood Transfusions

Blood transfusions frequently are required in the ED. At times the need is urgent, at other times less so. However, as observation units become more common, there is likely to be an increase in the number of non-urgent blood transfusions that are done while a patient stays in the ED. With this in mind, a review of the more common complications is appropriate.

Infectious Disease Issues and Blood Transfusion. Because of recent improvements in donor selection, serologic testing of donated blood, and viral inactivation procedures, the blood supply within the United States has become relatively safe. However, it is difficult to imagine that the risk of transfusion related infections will ever be zero. With this in mind, patients will inquire about what risks are present if they need blood transfusion and the emergency medicine physician should be able to give this information.

After the initial screening of blood donors, the blood is then screened for syphilis, hepatitis B and C, human T-lymphotropic virus type I, HIV-1, and HIV-2.[25] Nine selected blood products also are screened for cytomegalovirus.

Despite screening and viral inactivation procedures, some risks remain with transfusion. At present, it is estimated that from 1 in 450,000 to 1 in 660,000 donors may transmit HIV.[26,27] Transmission of disease is now thought to occur almost exclusively in the window of time between infection and an individual testing positive for antibodies. Hepatitis transmission remains a risk and there are no direct measures of exact rates. The current estimates for hepatitis B transmission are 1 in 63,000-500,000 and for hepatitis C they are 1 in 10,000-103,000.[21,28] Hepatitis C infection has a greater risk of transmission due to the difficulty in detecting a chronic infection. New tests are being developed. As for hepatitis A, cases of post-transfusion hepatitis A have been reported but are rare.

Bacterial contamination of blood can occur and exact rates, as well as the range of clinical outcomes, remain poorly defined.[29] Transfusion of red blood cells and platelets have been associated with bacterial contamination. In the case of red blood cells, bacterial sepsis most often is due to *Yersinia enterocolitica,* which grows easily in refrigerated blood. The risk of red blood cell-associated sepsis has been estimated to be 1 in 500,000 units transfused.[25]

Febrile Transfusion Reactions. This type of reaction is one of the more common transfusion-related problems. Febrile transfusion reactions are characterized by onset of fever at some point during a blood transfusion or within five hours of transfusion. The clinical presentation of this reaction can range from a mild elevation in temperature to fever along with rigors, headache, myalgias, vital sign abnormality, dyspnea, and chest pain.[25] *(See Table 4.)* In severe cases, it may be difficult to differentiate a febrile reaction from the more serious hemolytic transfusion reaction (discussed in a subsequent section) or sepsis.

Febrile transfusions most likely result from a combination of recipient antibody against donor leukocytes and cytokines that are produced during storage.[30] For the first-time febrile reaction, or in any severe reaction, the transfusion should be stopped and the product should be returned to the blood bank. Laboratory work as noted in the hemolytic transfusion section should be sent. Blood cultures should be obtained. The febrile transfusion reaction usually is self-limited and will respond to antipyretics. Premedication with diphenhydramine and acetaminophen may help prevent these reactions. For those patients with recurrent febrile reactions, the use of leukocyte-reduced blood products may be helpful.

Hemolytic Transfusion Reactions. These types of reactions can be acute or delayed. These reactions are the most common and are of the greatest concern. The delayed responses are less common and are the result of an amnestic response to an antigen to which the recipient already is sensitized. The antigenic stimulation in the individual with prior antigenic exposure results in antibody levels that can cause hemolysis.

The immediate hemolytic reactions most frequently are caused by ABO incompatibility. This incompatibility usually is the result of technical errors made during the collection or processing of blood, during pretransfusion testing, or during blood infusion.

When an acute reaction occurs most of the transfused cells are destroyed, which may result in activation of the coagulation system, release of anaphylotoxins, and other vasoactive amines.[31] Evidence of this type of reaction includes back pain, pain at the site of the transfusion, headache, alteration of vital signs (fever, hypotension, tachycardia), shortness of breath, evidence of developing disseminated intravascular coagulation, and evidence of developing renal failure. Evidence of hemolysis with hemoglobinemia and hematuria will be present. Serum haptoglobin will be decreased, lactate dehydrogenase will be elevated, and a direct Coomb's test will be positive.

Immediate treatment for an acute hemolytic transfusion reaction is to stop the transfusion upon first suspicion that this type of

Table 4. Febrile Transfusion Reactions

CLINICAL PRESENTATION:
Mild temperature elevation to fever
Rigors
Headache
Myalgias
Vital sign abnormality
Dyspnea
Chest pain
TREATMENT AND PREVENTION:
Antipyretics (premedication with diphenhydramine and acetaminophen may help prevent)
If recurrent, leukocyte-reduced blood products may be helpful

reaction is happening. The remaining blood should be sent, along with a post-transfusion blood specimen from the recipient, to the blood bank. The blood bank will be able to test the blood, review records, confirm blood types, and determine if the patient's syndrome is from a transfusion reaction. Urine also should be collected, and the blood work listed above may be sent to help confirm the diagnosis pending the results from the blood bank.

The patient will need to receive aggressive supportive care. It is critical to maintain renal blood flow with a combination of fluids, mannitol, and furosemide. Shock should be treated with pressors to support blood pressure. Coagulopathy should be treated with FFP and platelets. Steroids may be helpful.

Allergic Transfusion Reactions. This is another type of common transfusion reaction and is associated with onset of urticaria and puritis during the transfusion. Fortunately, only a small percentage of patients will have a more severe allergic reaction such as bronchospasm, wheezing, and true anaphylaxis. These reactions are caused by an immune response to plasma proteins.

Conservative therapy with an antihistamine usually will control the symptoms. The transfusion usually does not have to be stopped. For more severe symptoms, the transfusion may need to be stopped and more aggressive management initiated.

Transfusion-Related Acute Lung Injury. This is a transfusion-related complication that results in the appearance of bilateral pulmonary infiltrates, usually within four hours of transfusion.[32] This reaction is thought to occur due to the interaction between granulocytes and antibodies in the lung. The presentation will be similar to a patient with adult respiratory distress syndrome and diagnosis is made after ruling out other, more concerning etiologies for the lung findings. By itself, this lung injury is self limiting and generally resolves spontaneously with only supportive care.

Postsplenectomy State

A complete dialog on this topic is not possible in this format. However, it is included as a brief section to remind clinicians that many patients with hematologic disorders are either functionally asplenic, or have actually had the spleen removed due to complications of their disease. This fact can greatly increase the complexity of care for these already ill patients. It also is included because any person who has had his or her spleen removed has a hematologic abnormality and is at risk for the development of overwhelming infection. These infections are characterized by abrupt onset and progression of symptoms. Death may occur in as few as 6-12 hours and, unfortunately, the initial symptoms may be nonspecific. Enormous amounts of bacteria can accumulate in the blood and cerebrospinal fluid.[33] Septic shock with disseminated intravascular coagulation may develop as the infection proceeds. This syndrome is associated with high mortality rates.

Postsplenectomy prophylactic penicillin, pneumococcal vaccine, and meningococcal vaccine all should be given. If the emergency medicine physician finds a patient deficient in these immunizations, they should be given or the patient should be promptly referred. In those patients with a fever and no localizing focus, headache, drowsiness, or chills, septicemia should be suspected and the patient should be admitted. Aggressive, broad-coverage, intravenous antibiotics should be initiated after cultures have been obtained.[33]

References

1. Coyne MA, Lusher J. Guidelines for emergency care of the patient with hemophilia. *Emerg Med* 2000;32:69-78.
2. Hepatitis A among persons with hemophilia who received clotting factor concentrate—United States, September-December 1995. *MMWR Morb Mortal Wkly Rep* 1996;45:29-32.
3. Bona RD, Weinstein RA, Weisman SJ, et al. The use of continuous infusion of factor concentrates in the treatment of hemophilia. *Am J Hematol* 1989; 32:8-13.
4. Warrier I, Ewenstein BM, Koerper MA, et al. Factor IX inhibitors and anaphylaxis in hemophilia B. *J Pediatr Hematol Oncol* 1997;19:23-27.
5. Mannucci PM, Tuddenham EG. The hemophilias—From royal genes to gene therapy. *N Engl J Med* 2001;23:1773-1779.
6. Werner EJ. von Willebrand disease in children and adolescents. *Pediatr Clin North Am* 1996;43:683-707.
7. Morgan CH, Penner JA. Bleeding complications during surgery: Part I. Defects of primary hemostasis and congenital coagulation. *Lab Med* 1986;17:207-210.
8. Fowler WE, Berkowitz LR, Roberts HR. DDAVP for type IIB von Willebrand disease. *Blood* 1989;74:1859-1860.
9. Castillo R, Monteagudo J, Escolar G, et al. Hemostatic effect of normal platelet transfusion in severe von Willebrand disease patients. *Blood* 1991; 77:1901-1905.
10. Lukens JN. Sickle cell disease. *Dis Mon* 1981;27:1-56.
11. Bainbridge R, Higgs DR, Marde GH, et al. Clinical presentation of homozygous sickle cell disease. *J Pediatr* 1985;106:881-885.
12. Smith JA. Bone disorders in sickle cell disease. *Hematol Oncol Clin North Am* 1996;10:1345-1356.
13. Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med* 2000;342:1855-1865.
14. Lane PA. Sickle cell disease. *Pediatr Clin North Am* 1996;43:639-664.
15. Morris C, Vichinsky E, Styles L. Clinical assessment of acute chest syndrome in febrile patients with sickle cell disease: Is it accurate enough? *Ann Emerg Med* 1999;34:64-69.
16. Haberkern CM, Neumayr LD, Orringer EP, et al. Cholecystectomy in sickle cell anemia patients: Perioperative outcome of 364 cases from the National Perioperative Transfusion Study. Preoperative Transfusion in Sickle Cell Disease Study Group. *Blood* 1997;89:1533-1542.
17. Brown AK, Sleeper LA, Miller ST, et al. Reference values and hematologic changes from birth to 5 years in patients with sickle cell disease. Cooperative Study of Sickle Cell Disease. *Arch Pediatr Adolesc Med* 1994;148:796-804.
18. Emond AM, Collis R, Darvill D, et al. Acute splenic sequestration in

homozygous sickle cell disease: Natural history and management. *J Pediatr* 1985;107:201-206.
19. Pollack CV Jr. Emergencies in sickle cell disease. *Emerg Med Clin North Am* 1993;11:365-378.
20. Potter CG, Potter AC, Hatton CS, et al. Variation of erythroid and myeloid precursors in the marrow and peripheral blood of volunteer subjects infected with human parvovirus (B19). *J Clin Invest* 1987;79:1486-1492.
21. Serjeant GR, Serjeant BE, Thomas PW, et al. Human parvovirus infection in homozygous sickle cell disease. *Lancet* 1993;341:1237-1240.
22. Charache SL, Lubin B, Reid C. Management and therapy of sickle cell disease. NIH Publication. U.S. Department of Health and Human Services, September 1989;No. 85:2177.
23. Schrier SL. Hemoglobinopathies and hemolytic anemias. In: *Scientific American: Medicine.* Dale DC, Federman DD, eds. New York, NY: Healtheon/WebMD; 2000:(section 5)1-25.
24. Sackey K. Hemolytic anemia: Part 2. *Pediatr Rev* 1999;20:204-208.
25. Chamberland M, Khabbaz RF. Emerging issues in blood safety. *Infect Dis Clin North Am* 1998;12:217-229.
26. Lackritz EM, Satten GA, Aberle-Grasse J, et al. Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. *N Engl J Med* 1995;333:1721-1725.
27. Schreiber GB, Busch MP, Kleinman SH, et al. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *N Engl J Med* 1996;334:1685-1690.
28. Alter HJ. Residual risk of transfusion-associated hepatitis. In: NIH Consensus Development Conference on Infectious Disease Testing for Blood Transfusions. Bethesda, MD: National Institutes of Health; 1995:23-30.
29. Wagner SJ, Friedman LI, Dodd RY. Transfusion-associated bacterial sepsis. *Clin Microbiol Rev* 1994;7:290-302.
30. Davenport RD, Kunkel SL. Cytokine roles in hemolytic and nonhemolytic transfusion reactions. *Transfus Med Rev* 1994;8:157-168.
31. Labadie LL. Transfusion therapy in the emergency department. *Emerg Med Clin North Am* 1993;11:379-406.
32. Silliman CC, Paterson AJ, Dickey WO, et al. The association of biologically active lipids with the development of transfusion-related acute lung injury: A retrospective study. *Transfusion* 1997;37:719-726.
33. Lanzkowsky P. Hematologic emergencies. *Pediatr Clin North Am* 1979;26:909-930.

Physician CME Questions

25. Which of the following laboratory tests might be appropriate for a patient with a suspected bleeding disorder?
    A. Prothrombin time (PT)
    B. Activated partial thromboplastin time (aPTT)
    C. Complete blood count (CBC)
    D. All of the above

26. Inhibitors to clotting factors occur in what percentage of patients with hemophilia A?
    A. 1-2%
    B. 10%
    C. 20-25%
    D. Greater than 50%

27. Laboratory tests that may help diagnose a patient who is suspected of having von Willebrand's disease include which of the following?
    A. Factor VIII coagulant activity
    B. vWF antigen
    C. vWF activity
    D. Bleeding time
    E. All of the above

28. In the patient with sickle cell anemia, if the white cell count has a left shift and is elevated above 20,000 WBCs/mm^3, which of the following is a likely cause?
    A. Infection
    B. Pulmonary abnormality
    C. Bone infarct
    D. Papillary necrosis

29. Which of the following statements is correct regarding the sickle cell patient with acute chest syndrome?
    A. The exact etiology is unclear, but infection, infarction, and fat embolism all have been implicated.
    B. The initial chest radiograph is positive for pulmonary involvement greater than 90% of the time.
    C. There is no therapy for acute chest syndrome.
    D. Pneumonia easily can be distinguished from pulmonary infarction on the chest radiograph.
    E. All of the above

30. Which of the following has been implicated as a cause of aplastic crisis in the patient with sickle cell disease?
    A. Parvovirus
    B. Folate deficiency
    C. Bone marrow necrosis
    D. Frequent blood transfusions
    E. Only A, B, and C

31. Which of the following could be expected in a patient with beta-thalassemia major?
    A. Elevated MCV
    B. Low RDW
    C. Nucleated red cells
    D. Macrocytic red blood cells

32. Which of the following statements is correct regarding blood transfusions?
    A. It is estimated that from 1 in 450,000 to 1 in 660,000 donors may transmit HIV.
    B. Cases of port-transfusion hepatitis A transmission have been reported but are rare.
    C. In the case of red blood cells, bacterial sepsis most often is due to *Yersinia enterocolitica.*
    D. Hepatitis C transmission occurs more frequently than hepatitis B transmission.
    E. All of the above

In Future Issues:

Thoracic Trauma: Part I