Emergency Management of Red Blood Cell Disorders

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**PERSPECTIVE**

The red blood cell (RBC) disorders include a distinct group of disease entities that are diverse in presentation yet similar in their emergency diagnosis and management. These disorders include anemia (acute, chronic), sickle cell anemia, and polycythemia vera (PV). Patients with both malignant and nonmalignant hematologic disease may present with dramatic and often life-threatening complications. Emergency management of these disorders requires a thorough understanding of the underlying pathologic processes, as well as a concise and systematic approach to diagnosis, stabilization, and treatment.

**ANEMIA**

**EPIDEMIOLOGY**

Anemia is more common than is generally realized. The World Health Organization defines anemia as a condition characterized by hemoglobin (Hgb) levels lower than 13 g/dL in men or lower than 12 g/dL in women. Data from the National Center for Health Statistics that likely underestimate the frequency of anemia indicated that approximately 3.4 million U.S. residents have anemia, and that the groups with the highest prevalence are women, African Americans, older persons, and those with the lowest incomes. Using laboratory data from the general U.S. population, the second National Health and Nutrition Survey reported anemia to be the most prevalent in infants, teenage girls, young women, and older men. In another survey, the prevalence of anemia declined significantly among U.S. women and children from 1988 to 2002, but the cause of this decline was unknown. In persons 65 years and older, anemia was present in 11.0% of men and 10.2% of women, and the prevalence rose to more than 20% in people 85 years and older. One third of the cases of anemia were the result of nutritional deficiencies, and one third of cases were secondary to chronic illness, including but not limited to chronic renal disease.
**PATHOPHYSIOLOGY**

Anemia is classified into three broad categories: (1) disorders of decreased RBC production, (2) disorders of increased RBC destruction, and (3) disorders resulting from RBC loss. Disorders in each of these categories may manifest differently and ultimately have their own management approaches (Table 204.1).

RBCs, or erythrocytes, contain fluid Hgb encased in a lipid membrane and are the predominant cellular component of blood. RBCs make up 45% of the blood volume and are responsible for carrying oxygen from the lungs to the peripheral tissues. A 70-kg person has approximately 30 trillion RBCs, resulting in approximately 300 million RBCs in each drop of blood. The normal RBC is composed of three types of Hgb: Hgb A (97%), Hgb F (1%) or fetal Hgb, and Hgb A2 (2%)

Hgb A is composed of two β-globin chains and two α-globin chains bonded to four iron-containing heme groups. Hgb production requires iron, the synthesis of the protoporphyrin ring, and the production of the globin chains. Reductions in any of these processes result in anemia.

RBC precursors develop in bone marrow at rates usually determined by the body’s demand for sufficient circulating Hgb to oxygenate tissues adequately. Once produced, the mature RBC remains in circulation for approximately 120 days before it is engulfed and destroyed. Given the life span, chronic anemias that are caused by RBC underproduction generally develop and progress slowly over weeks to months. In contrast, acute anemias that are caused by bleeding or hemolysis generally occur rapidly over days to weeks. The tempo of anemia development depends on the pace of bleeding or hemolysis in relation to RBC production. The aggressiveness of intervention and management depends on the acuteness of onset and the severity of the clinical presentation.

**PRESENTING SIGNS AND SYMPTOMS**

Because anemia either can be a primary disorder or can occur secondary to other systemic processes, a careful history and physical examination provide valuable insight into the potential cause. All patients require a focused yet thorough history. For critically ill and noncommunicative patients, the history

### Table 204.1 Classification of Anemia

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>CLASSIFICATION</th>
<th>DISEASE PROCESS</th>
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<tbody>
<tr>
<td>Decreased RBC production</td>
<td>Microcytic</td>
<td>Iron deficiency&lt;br&gt;Thalassemia&lt;br&gt;Sideroblastic&lt;br&gt;Chronic disease (neoplasm, infection, diabetes, uremia, thyroid disease, cirrhosis)</td>
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<tr>
<td>(hypoproliferative)</td>
<td></td>
<td></td>
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<tr>
<td>Normocytic</td>
<td></td>
<td>Primary bone marrow problem (aplastic, myeloid metaplasia, myelofibrosis, myelophthisic anemia, Diamond-Blackfan anemia)</td>
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<tr>
<td>Macrocytic</td>
<td></td>
<td>Folic acid deficiency&lt;br&gt;Liver disease&lt;br&gt;Vitamin B12 deficiency&lt;br&gt;Scurvy&lt;br&gt;Hypothyroidism&lt;br&gt;Chemotherapy, immunosuppressive therapy</td>
</tr>
<tr>
<td>Increased RBC destruction</td>
<td>Intrinsic</td>
<td>Membrane disorder (spherocytosis, sickle cell, stem cell disorder, elliptocytosis, spur cell)</td>
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<tr>
<td>(hemolytic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrinsic</td>
<td></td>
<td>Hemoglobin disorder (thalassemia, autoimmune, hemoglobinopathies)&lt;br&gt;Infections (hepatitis and cytomegalovirus, Epstein-Barr virus, typhoid fever, Escherichia coli)&lt;br&gt;Medications (penicillin, antimalarials, sulfa drugs, or acetaminophen)&lt;br&gt;Leukemia or lymphoma&lt;br&gt;Autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis, Wiskott-Aldrich syndrome, ulcerative colitis)&lt;br&gt;Enzyme defect (G6PD)</td>
</tr>
<tr>
<td>RBC loss (hemorrhagic)</td>
<td>Acute or chronic</td>
<td>Gastrointestinal tract&lt;br&gt;Traumatic&lt;br&gt;Intraperitoneal&lt;br&gt;Extrapерitoneal&lt;br&gt;Gynecologic&lt;br&gt;Urinary&lt;br&gt;Pelvic&lt;br&gt;Drug related&lt;br&gt;Epistaxis, hemoptysis</td>
</tr>
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</table>

G6PD, Glucose-6-phosphate dehydrogenase; RBC, red blood cell.
should be obtained from caretakers, paramedics, or primary care physicians.

The extent of the symptoms, whether mild or life-threatening, depends on several contributing factors. If anemia develops acutely, compensatory adjustments may not have enough time to take hold, and consequently, the patient may have more pronounced symptoms than if the anemia developed over weeks to months. Furthermore, underlying chronic comorbidities such as myocardial ischemia and transient cerebral ischemia may be unmasked in the presence of anemia.

**ACUTE ANEMIA**

Patients with anemia resulting from acute bleeding present with hypovolemia. The combined effects of hypovolemia and anemia may cause tissue hypoxia or anoxia through diminished cardiac output, resulting in decreased oxygen-carrying capacity (anemic hypoxia). When the Hgb concentration falls to less than 7.5 g/dL as a result of losses ranging from 5% to 15% in blood volume, the resting cardiac output rises significantly, with an increase in both heart rate and stroke volume. These patients are symptomatic at rest and may be aware of this hyperdynamic state; they often complain of palpitations, lightheadedness, dizziness, or a pounding pulse. Larger losses cause progressive increases in heart rate, decreases in arterial blood pressure, and evidence of organ hypoperfusion. Hypovolemic shock is seen when vital organ systems such as the kidneys, the central nervous system, and the heart are affected. In the emergency department (ED), a source of blood loss may be readily apparent on evaluation (e.g., trauma with hemorrhage from the extremities, gastrointestinal bleeding, menstrual blood loss); however, this may not be the case in, for example, aortic dissection or retroperitoneal hemorrhage.

Mild to moderate hypovolemia may be tolerated in the young patient. In older patients, however, these responses are modified by the rapidity of blood loss and by characteristics such as comorbid illnesses, preexisting volume status, Hgb values, and the use of medications that have cardiac or peripheral vascular effects (e.g., beta-blockers, antihypertensive agents). Therefore, the emergency physician (EP) should elicit a thorough and focused history, including medications, while assessing the airway, stabilizing breathing, and initiating resuscitation as needed.

**CHRONIC ANEMIA**

Because anemia can be a primary disorder or can occur secondary to hypoproliferation or chronic blood loss, a careful history and physical examination provide valuable insight into the potential cause. Individuals with mild anemia are often asymptomatic and are able to sustain a relatively normal level of function at Hgb levels that are significantly lower than normal. Other patients may present with myriad nonspecific symptoms (Box 204.1). Because fatigue is nonspecific, determining the concomitant presence of a systemic inflammatory disorder, infection, or malignant disease may be critical in determining the underlying causes of anemia.

Past medical history is quite informative. For instance, a history of diabetes mellitus is associated with significantly impaired renal production of erythropoietin.6 Certain medications are associated with bone marrow depression. Therefore, all pharmacologic agents, both prescribed drugs and over-the-counter agents, including alternative medications, should be reviewed. Occupational history is relevant, as in the case of welders, who may have been exposed to lead or other agents potentially toxic to the bone marrow. Social history is important because a history of intravenous drug use may suggest the possibility of human immunodeficiency virus infection, which can be associated with anemia.7 Dietary history is relevant. For example, the finding of pica in adults (most commonly from the ingestion of nonfood items) is well known to be associated with iron deficiency anemia. A family history of anemia is important; for example, adults with congenital hereditary spherocytosis often develop symptoms later in life.

Physical findings in either acute or chronic anemia are myriad and often nonspecific, and they may relate to the underlying disease process and the duration (Table 204.2). Pathognomonic findings are not the norm. Furthermore, patients with chronic anemia usually do not have the typical physical findings associated with acute anemia.

### Box 204.1 Chronic Anemia

<table>
<thead>
<tr>
<th>Finding</th>
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<tbody>
<tr>
<td>Fatigue</td>
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<td>Weakness</td>
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<tr>
<td>Irritability</td>
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<tr>
<td>Headache</td>
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<td>Dizziness (vertigo, especially postural)</td>
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### Table 204.2 Physical Findings in Anemia

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>FINDING</th>
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<tbody>
<tr>
<td>Skin</td>
<td>Pallor Usefulness limited by color of skin, Hgb concentration, and fluctuation of blood flow to skin Palmar crease color a better indicator, if as pale as surrounding skin, Hgb usually &lt;7 g/dL</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Purpura, petechiae, and jaundice</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia Wide pulse pressure Orthostatic hypotension Hyperdynamic precordium Systolic eject murmur over pulmonic area</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea Rales</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Hepatomegaly and/or splenomegaly Ascites Masses Positive result on Hemoccult test</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Pale conjunctiva Scireral icterus Retinal hemorrhages</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Peripheral neuritis or neuropathy Mental status changes</td>
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</tbody>
</table>

**Note:** Hgb, Hemoglobin.
The first step in approaching anemia is to classify the process as microcytic (MCV < 80 fL), normocytic (MCV, 80 to 100 fL), or macrocytic (MCV > 100 fL). Clues to the diagnostic possibilities for the three major classes are listed in Table 204.3.

Along with anemia, another characteristic laboratory feature of hemolysis is reticulocytosis, the normal response of the bone marrow to the peripheral loss of RBCs. Patients with aplastic anemia or some other insult to the bone marrow from drugs or toxins have a reduced reticulocyte count. Some patients require special correction of their reticulocyte count (see the “Facts and Formulas” box).

Blood type and cross should be sent to the blood bank so that type-specific or type-matched and crossmatched blood can be readied. Other tests to obtain are unconjugated bilirubin and lactate dehydrogenase. These values are increased when RBCs are destroyed. In patients with severe intravascular hemolysis, the binding capacity of haptoglobin is exceeded rapidly, and free Hgb is filtered by the glomeruli, thus leading to decreased haptoglobin and increased hemoglobinuria or urobilinogen levels.

Imaging studies are disease specific and depend on the patient’s symptoms. Chest radiographs are indicated in all patients with significant anemia. Cardiomyopathy may be present in patients with chronic anemia. An electrocardiogram is required for older patients, those with chest pain, patients with profound anemia, or those who have an underlying disease or increased risk factors for cardiac ischemia. Patients with blood loss may benefit from an ultrasound examination, which is a quick, noninvasive, and relatively simple bedside test useful for diagnosing intraperitoneal bleeding. The focused abdominal sonography for trauma (FAST) examination detects blood in the hepatorenal fossa, paracolic gutters, splenorenal area, and pelvis. Ultrasound is
also useful for detecting pregnancy-related bleeding, especially that emanating from a ruptured ectopic pregnancy. Stable patients with intraabdominal blood loss benefit from computed tomography (CT) scanning. CT scanning has sensitivities similar to those of ultrasound, yet it identifies causes, including retroperitoneal, pelvic, and subcapsular sites, more clearly.

A nasogastric tube may be indicated in the acute setting to diagnose and manage an ongoing upper gastrointestinal hemorrhage. Bile must be aspirated to rule out bleeding proximal to the ligament of Treitz. Once upper gastrointestinal bleeding is established, esophagogastroduodenoscopy is the study of choice for determining the source of bleeding and for treatment. Emergency esophagogastroduodenoscopy can be performed in the ED, and its use is indicated in the hemodynamically unstable patient. Consultation with a gastroenterologist is required. Sigmoidoscopy or colonoscopy may be useful in diagnosing and treating lower gastrointestinal bleeding, but it is rarely helpful in the acute setting.

TREATMENT

After anemia is identified by a CBC determination in the ED, management is aided by an approach that categorizes anemia as a symptom caused by the decrease in Hgb, rather than as an isolated diagnosis (see the “Priority Actions” box). Like fever, anemia is a symptom of disease that requires investigation to determine the underlying origin.

**PRIORITY ACTIONS**

1. Determine the patient’s hemodynamic status. The need for transfusion is often limited to those in hypovolemic shock.
2. If the patient is unstable, initiate resuscitation with crystalloids.
3. Once the patient is stabilized, blood transfusions are widely used as a rapid and effective therapeutic intervention in the context of either severe anemia (Hgb < 8.0 g/dL) or life-threatening anemia (Hgb < 6.5 g/dL).
4. Look for the underlying cause and attempt to correct it.

Hgb, Hemoglobin.

Patients with long-standing or chronic anemias are able to compensate and do not require transfusion, especially if the Hgb is greater than 9.0 g/dL. Patients who are expected to respond to the administration of a specific agent such as folic acid, iron, or vitamin B₁₂ can usually be spared transfusions. If the anemia has precipitated an episode of congestive heart failure or myocardial ischemia, prompt administration of packed RBCs is indicated. For some patients in the ED, treatment can be begun without waiting for a definitive outpatient evaluation. For example, prenatal vitamins and iron replacement can be begun in the pregnant patient with anemia. In symptomatic pregnant patients, parenteral iron is preferred. Megaloblastic anemia resulting from folic acid or vitamin B₁₂ deficiency can be treated with parenteral cobalamin (1000 g/day) or oral folic acid (1 mg/day). Erythropoietin therapy remains an option for patients undergoing elective surgical procedures or receiving chemotherapy and in patients with chronic heart failure or acquired immunodeficiency syndrome. In the acute setting, however, specifically in symptomatic heart failure, the role of erythropoietin therapy remains to be defined.

**DISPOSITION**

Fortunately, most patients have chronic anemia without blood loss and can be managed conservatively. In many cases, acute interventions and drug therapy are not indicated in the ED, and patients can be referred for follow-up to their primary care physicians.

Emergency consultation and hospital admission are required for patients presenting with hypovolemia or active bleeding who demonstrate a considerable drop in Hgb and hematocrit values when compared with previous values. A Hgb value of less than 8.0 g/dL in a symptomatic patient is enough to warrant admission for replacement of blood products. Patients who have underlying disease such as cardiac ischemia or congestive heart failure and who are now symptomatic and complaining of chest pain, tachypnea, or shortness of breath because of their anemia also require admission. Patients with new-onset or worsening pancytopenia require urgent consultation. Finally, admission is indicated for those patients who may not comply with follow-up or those in whom the clinician anticipates the need for an extensive work-up. Admission is to a medical ward bed, intermediate unit, or intensive care bed, depending on the patient’s presenting symptoms.

**SICKLE CELL ANEMIA**

**EPIDEMIOLOGY**

Sickle cell disease (SCD), characterized by lifelong hemolytic anemia and many different painful and debilitating vasoocclusive events, occurs in 70,000 to 80,000 U.S. residents of African, Mediterranean, or Middle Eastern descent. In the United States, the life expectancy for patients with SCD is shortened by approximately 30 years, whereas in Africa, where comprehensive medical care is less readily available, death in early childhood is usual. Eight percent of African Americans are heterozygous carriers of the sickle cell trait; approximately 40% of their Hgb is Hgb S. They do not have anemia and need neither treatment nor occupational restrictions.

**PATHOPHYSIOLOGY**

SCD is an inherited condition caused by a point mutation in the β-globin gene (Hgb B) that causes the substitution of valine for glutamic acid at position 6 of the β-globin chain (Glu6Val). This mutation results in the abnormal Hgb S (Fig. 204.1). When deoxygenated, Hgb S polymerizes, thus damaging the sickle RBC. These sickle cells are short-lived.
and interact with endothelial cells, WBCs, platelets, and other plasma components to initiate the vasoocclusive manifestations associated with SCD. Among hemolytic anemias, the vasoocclusive features of SCD are unique. By occluding small blood vessels and sometimes large vessels, sickle cells cause vascular injury (Fig. 204.2).

**PRESENTING SIGNS AND SYMPTOMS**

Vasoocclusion, which is responsible for most of the severe complications of SCD, can occur wherever blood flows. The clinical features of SCD are outlined in Table 204.4.

**PAINFUL EPISODES**

Acute painful crisis in SCD is a frequent complication and considerably diminishes the quality of life of patients with this disease. Approximately 60% of patients have an episode of severe pain. A few patients have severe pain almost constantly. Episodes of pain are sometimes triggered by infection, extreme temperatures, or physical or emotional stress, but more often they are unprovoked and begin with little warning.

**ACUTE CHEST SYNDROME**

The *acute chest syndrome* is the leading cause of death and hospitalization among patients with SCD. Affecting approximately 40% of all patients with sickle cell anemia, it is the second most common reason for hospitalization and the leading cause of intensive care unit admission and premature death in patients with SCD. Its cardinal features are fever, pleuritic chest pain, referred abdominal pain, cough, lung infiltrates, and hypoxia. It is most common but least severe in children, can occur postoperatively, and when recurrent, can lead to pulmonary hypertension, restrictive lung disease, and eventually right-sided heart failure and death.

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**Table 204.4 Clinical Complications of Sickle Cell Disease**

<table>
<thead>
<tr>
<th>TYPE</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoocclusive complications</td>
<td>Pain crises, Acute chest syndrome, Splenic sequestration, Cerebrovascular crisis, Priapism, Liver disease, Leg ulcers, Spontaneous abortion, Osteonecrosis, Renal crisis, Retinopathy</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>Osteomyelitis, <em>Escherichia coli</em> sepsis, <em>Streptococcus pneumoniae</em> sepsis</td>
</tr>
<tr>
<td>Hemolytic complications</td>
<td>Choleithiasis, Anemia, Aplastic anemia</td>
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</table>
Asthma has been associated with multiple complications of SCD, including acute chest syndrome. Asthma is an independent risk factor for mortality in children with SCD, and it confers a twofold higher risk of death.18

CEREBROVASCULAR CRISIS
Cerebrovascular disease is the second leading cause of mortality and a common cause of morbidity in sickle cell anemia: approximately 10% of patients have a clinical stroke by age 20 years, and another 22% have evidence of silent infarction on magnetic resonance imaging. Manifestations of neurologic complications may include overt clinical stroke or subtler neuropsychological abnormalities often associated with subclinical stroke. Risk factors for ischemic stroke presentation in SCD include prior transient ischemic attacks, a decrease in steady-state Hgb, a history of acute chest syndrome, and an increase in systolic blood pressure. Risk factors for hemorrhagic stroke include a decrease in steady-state Hgb and an increase in steady-state WBC.

RIGHT UPPER QUADRANT SYNDROME
Right upper quadrant syndrome is manifested by any or all of the following features: hyperbilirubinemia, abdominal pain, fever, right upper quadrant abdominal tenderness, hepatomegaly, abnormalities on liver function testing, and hepatic failure. Possible causes include choledolithiasis, viral hepatitis, biliary cholestasis, and hepatic ischemia. Cholelithiasis occurs in children as young as 3 to 4 years of age and is eventually found in approximately 70% of patients; this condition often necessitates cholecystectomy once right upper quadrant pain is identified.

The three acute hepatic syndromes seen in SCD are acute hepatic cell crisis, acute hepatic sequestration crisis, and sickle cell intrahepatic cholestasis. Intrahepatic cholestasis is benign and may be associated with severe hyperbilirubinemia that resolves in 7 to 10 days, especially in children. A syndrome more common in adults is associated with fever, leukocytosis, abdominal pain, and deteriorating liver function, as indicated by measurement of liver enzymes. This hepatic crisis usually progresses to hepatic failure, coagulopathy, encephalopathy, and death.

PRIAPISM
Priapism is a sustained, painful, and unwanted erection of the penis that pathophysiologically is the result of an accumulation of sickled RBCs in the corpora cavernosa that cause ischemia or low flow. Approximately 30% of male patients with SCD who are less than 20 years old report at least one episode of priapism, whereas frequencies of 30% to 45% are estimated for adult men. This condition is most common in patients with the greatest amount of hemolysis. Postpubertal male patients tend to have more prolonged episodes of priapism and have a less favorable prognosis for future potency. One sequel is impotence; therefore, for the EP, the utmost priority in these patients is detumescence, especially within the first 12 hours.

SPLENIC SEQUESTRATION
Splenocirculation, caused by sickled cells trapped in the splenic circulation, results in precipitous decreases in Hgb concentration and rapid enlargement of the spleen. This condition may be life-threatening. It is common in infants and young children and is less common in older children and adults because the spleen is significantly fibrotic in these patients by the age of 5 years. Acute splenic sequestration crisis generally is defined as an acute drop in Hgb levels (>2 g/dL) associated with splenomegaly, reticulocytosis, and signs of intravascular volume depletion. Drops in Hgb levels greater than 4 g/dL are associated with 35% mortality. Splenic sequestration carries a 15% mortality rate and is the second leading cause of death among children. It may manifest as hypotension (caused by shock from worsening anemia) associated with an enlarged, tender spleen. Fatigue, listlessness, and pallor have also been described. An association between this crisis and acute viral infections exist, especially parvovirus B19 infection.

TRANSIENT APLASTIC CRISIS
Aplastic crisis occurs in children with sickle cell anemia in response to transient suppression of erythropoiesis, most often because of infection with parvovirus B19, the same etiologic agent that causes erythema infectiosum (“fifth disease”). This crisis is usually a unique event in the life of a patient and suggests the induction of long-lasting, protective immunity. Although self-limited, aplastic crisis can cause severe, occasionally fatal, anemia that precipitates congestive heart failure, cerebrovascular accidents, and acute splenic sequestration. WBC and platelet counts may fall somewhat during transient aplastic crisis, especially in patients with functioning spleens. Aplastic crisis may be also be precipitated by other infections, including infections with Streptococcus pneumoniae, other streptococci, Salmonella, and Epstein-Barr virus. Children present with signs of severe anemia, such as tachycardia and pallor.

STREPTOCOCCUS PNEUMONIAE SEPSIS
The incidence of invasive S. pneumoniae infection is 20- to 100-fold higher in children with SCD than in the general population. Penicillin prophylaxis for children with sickle cell anemia reduces the incidence of invasive pneumococcal infection by 84%, independent of pneumococcal immunization status.

DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC TESTING
Patients with SCD frequently require immediate medical attention because of the severity of their disease and its potential complications. Understanding the various presenting symptoms and staying alert for severe manifestations of the disease are important for EPs (see the “Priority Actions” box). Diagnostic testing is often focused, depending on the presenting symptoms. In most patients, however, a basic set of laboratory tests should be obtained. Baseline laboratory values are helpful, as well as knowledge of the patient’s medication history, the severity and frequency of previous crisis, and any surgical complications.

Emergency management depends on clinical presentation and can be symptom specific. Patients with known SCD should have a CBC and a reticulocyte count. These tests are necessary to help screen for severe anemia, aplastic crisis, sequestration crisis, and infection. A major drop in Hgb (e.g., >2 g/dL) from baseline values indicates a hematologic crisis.
Hematocrit of 20% to 30%), accompanied by a left shift and significant bandemia. In interpreting these values, the EP should know that most patients with SCD have chronic anemia. Patients with chest pain require an electrocardiogram to establish a baseline and to diagnose acid-base abnormalities, including productive cough and tachypnea. The urine must be examined for evidence of infection if the patient has fever or signs of urinary tract infection. Hematuria and isosthenuria are often present in patients with SCD. If signs of urinary tract infection are present, a urine Gram stain and culture should be obtained. Patients with fever without clear evidence of pneumonia, cholecystitis, pyelonephritis, or apparent source require blood cultures, preferably with hydration, analgesia, ice packs, and exchange transfusions.

Imaging studies are also symptom specific. A chest radiograph is indicated in all patients with respiratory symptoms, including productive cough and tachypnea. Radiographic findings in acute chest syndrome may be normal in the early stages of presentation. Bone radiographs are necessary in patients with localized bony pain if osteomyelitis is suspected. Although not readily available in the ED, bone scans may be used to confirm the diagnosis. Ultrasonography is necessary in patients with abdominal pain to rule out cholecystitis, cholelithiasis, hepatomegaly, and splenomegaly. Patients with new neurologic signs and symptoms require CT scanning or magnetic resonance imaging of the head.

If the reticulocyte count is normal, splenic sequestration is the probable cause. If the reticulocyte count is low, bone marrow failure is the probable cause. An infection is indicated by major elevations in the WBC count (e.g., >15,000/mm³) accompanied by a left shift and significant bandemia. In interpreting these values, the EP should know that most patients with SCD have chronic anemia. Patients with chest pain require an electrocardiogram to establish a baseline and to diagnose acid-base abnormalities. Continuous pulse oximetry monitoring is warranted and reliable.

A type and crossmatch are sent to the blood bank, in case transfusion is required. Measurement of prothrombin and partial thromboplastin times are indicated to evaluate for hypercoagulable states, especially in patients demonstrating evidence of thrombotic disease, including stroke, and myocardial ischemia.

Patients with abdominal pain require liver function tests and serum lipase evaluations. An elevated baseline indirect bilirubin level may be normal because of chronic hemolysis. Extreme elevation may indicate cholelithiasis and cholecystitis. Patients with chest pain require an electrocardiogram to screen for myocardial ischemia.
TREATMENT

Treatment of SCD is evolving. The description of barriers to effective pain management is interesting and has been well documented. EPs tend to undertreat their patients because they fear patients’ dependence on pain medication, which in reality is present in only 1% to 3% of patients. Patients with SCD who are in pain are also misunderstood because they display a different attitude to their severe pain than do trauma or oncology patients. Although patients with SCD complain of severe pain, they may engage in activities that are inconsistent with the traditional image of the patient in severe pain, such as watching television or talking on the telephone. These patients are therefore often perceived as exaggerating their pain to receive additional narcotics, whereas these activities may actually be learned distractions or coping mechanisms. Another example is the sleeping patient who, when awakened, reports unrelenting pain. This situation may stem from an imbalance between the sedative and analgesic effects of opiates or a need for sleep despite the pain. The result is a lack of trust between patients and health care providers. In centers specializing in sickle cell crises, the attitudes toward pain tend to be better understood, and treatment outcomes are superior, compared with EDs.

Oral analgesics suffice for treating mild to moderate pain. Patients with mild to moderate pain seem to find no difference between intravenous and oral morphine. Most opiates have comparable efficacy and safety profiles, but morphine (0.1 mg/kg) is considered the drug of choice for treatment of acute sickle cell pain. Hydromorphone (1.5 mg) may be used if morphine is unable to achieve effective analgesia. In children, studies emphasize oral dosing of potent opioids (weight-based dosing) and nonsteroidal antiinflammatory drugs, home treatment, and reduced reliance on EDs departments or inpatient admission. A pain protocol, if available, should be used (Box 204.2). ED-based pain management protocols have been shown to decrease ED visits and hospitalizations and to increase use of primary care clinics by patients with SCD.

Patients in severe pain should be given an opiate parenterally and preferably initiated within 15 to 20 minutes. The opiate should be dosed at frequent (15 to 30 minutes), fixed intervals, not as needed, until the pain has diminished, at which time the dose of the opiate can be tapered and then stopped, and oral analgesic therapy can be instituted. When available and appropriate for the treatment of acute pain, patients prefer patient-controlled analgesia (PCA) to scheduled dose or continuous infusion of morphine. When used to treat acute pain episodes, PCA results in similar pain relief with lower morphine consumption when compared with continuous infusion of morphine. Furthermore, when introduced in the ED for the treatment of acute pain, PCA use was associated with a shorter elapsed time between onset of pain and treatment. These data, along with clinical experience, suggest that PCA has emerged as a standard for the treatment of acute pain, and, if possible, it should be started in the ED.

The use of meperidine is discouraged because of the risk of seizures. Many opioid side effects can be ameliorated by drug therapy directed at the side effect (e.g., antiemetics to treat nausea and vomiting, antihistamines to treat itching, laxatives to treat constipation). Antiinflammatory drugs and intravenous methylprednisolone may provide an opiate-sparing effect, but concern exists about their negative effects on bone healing. In addition, painful crises seem to recur frequently after treatment with methylprednisolone.

Urgent replacement of blood is often required for sudden severe anemia occurring in children when blood is sequestered in an enlarged spleen or when parvovirus B19 infection causes transient aplastic crisis. For aplastic crisis, clinical management is supportive and depends on the degree of anemia and cardiovascular compromise. Simple transfusions are administered to raise the Hgb to approximately 10 g/dL and the hematocrit to approximately 30% if the reticulocyte count is less than 1% to 2% with no signs of spontaneous recovery. Increasing the Hgb level to more than 11 g/dL is not recommended because of increased viscosity and risk of vaso-occlusion. For shock caused by splenic sequestration, emergency management is aimed at restoring circulating blood volume and hemodynamic stability through the infusion of crystalloids and volume expanders and by repeated simple or exchange blood transfusions. Ultimately, splenectomy may be performed because sequestration has been shown to recur in 50% of patients and represents a life-threatening event. Admission is required for patients with aplastic crisis and

<table>
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<th>BOX 204.2 Emergency Department–Based Pain Protocol</th>
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<tr>
<td>• Determine patients’ previous known requirement for analgesia.</td>
</tr>
<tr>
<td>• Determine drug allergies and document the type of reaction.</td>
</tr>
<tr>
<td>• All patients should receive ibuprofen, 600 mg PO × one dose, unless a contraindication exists.</td>
</tr>
<tr>
<td>• Morphine is the drug of choice; hydromorphone is preferred in morphine-allergic patients.</td>
</tr>
<tr>
<td>• Evaluate pain: patients with severe pain requiring IV opioids or moderate pain able to take PO opioids.</td>
</tr>
<tr>
<td><strong>Severe Pain</strong></td>
</tr>
<tr>
<td>• Administer morphine, 5 to 10 mg IV initial dose, then 4 to 6 mg every 5 to 10 minutes, or hydromorphone, 1.5 mg IV initial dose, then 0.5 to 1 mg IV every 5 to 10 minutes.</td>
</tr>
<tr>
<td>• Titrate to comfort.</td>
</tr>
<tr>
<td>• Start IV PCA.</td>
</tr>
<tr>
<td>• If PCA demands fewer than 3, wean off IV PCA, and discharge with a standing dose of ibuprofen, Percocet (acetaminophen and oxycodone), morphine SR, or hydromorphone.</td>
</tr>
<tr>
<td>• If PCA demands more than 3, admit the patient.</td>
</tr>
<tr>
<td><strong>Moderate Pain</strong></td>
</tr>
<tr>
<td>• Administer morphine liquid, 10 mg PO × one dose or hydromorphone tablet, 2 mg PO × one dose.</td>
</tr>
<tr>
<td>• Reassess at 10 minutes.</td>
</tr>
<tr>
<td>• If no relief occurs, treat with IV opioids.</td>
</tr>
<tr>
<td>• If relief occurs, discharge the patient with a standing dose of ibuprofen, Percocet (acetaminophen and oxycodone), morphine SR, or hydromorphone.</td>
</tr>
</tbody>
</table>

IV, Intravenously(ly); PCA, patient-controlled analgesia; PO, orally; SR, sustained release.
splenic sequestration. Transfusions are not needed for the usual anemia or episodes of pain associated with SCD.

Treatment of acute chest syndrome is supportive and may include supplemental oxygen to maintain arterial oxygen saturation at more than 92%. Analgesia and incentive spirometry can minimize chest wall splinting and thus prevent atelectasis and hypoxemia. Pulse oximetry in patients with SCD has been shown to correlate with arterial oxygen content. Antibiotics should be given to treat infections with S. pneumoniae, Haemophilus influenzae, and atypical organisms such as Mycoplasma, Legionella, and Chlamydia. Frequently, a macrolide with a third-generation cephalosporin is chosen. In acute chest syndrome, simple transfusion has been demonstrated to be more effective than exchange transfusion.

Given the increased proclivity of patients with SCD to develop alloantibodies, the potential negative effects of a higher Hgb level after exchange, and the time and the expense of both the pheresis procedure and the vascular access insertion, EPs should initiate simple transfusions first in the event that the Hgb is less than 30%.

Acute hepatic cell crisis manifests with tender hepatomegaly, worsening jaundice, and fever. This syndrome usually resolves within 3 to 14 days with supportive care alone, but it can progress to liver failure, which carries a dismal prognosis. Exchange transfusion should be considered for patients with signs of progressive liver dysfunction.

Sepsis is a leading cause of death, especially in younger children. Management incorporates the following: (1) treatment of the infection with source control and antimicrobial agents; (2) rapid and targeted resuscitation from shock with administration of fluid (and, if appropriate, blood products), vasopressors, or inotropic agents; (3) adjuvant therapy with recombinant human activated protein C or corticosteroids in carefully selected patients; and (4) supportive measures such as lung-protective ventilation for acute respiratory distress syndrome. Appropriate cultures of blood and material from other sites should be quickly obtained, and broad-spectrum intravenous antibiotics should be started within the first hour after severe sepsis or septic shock is recognized. All patients who have high fevers and who are not receiving prophylactic penicillin should receive intravenous ceftiraxone as a precaution against meningitis from S. pneumoniae and Neisseria meningitidis. Patients with osteomyelitis should be treated for infection with Salmonella and Staphylococcus aureus. Patients with presumed urinary tract infections, especially pylonephritis, should receive treatment for Escherichia coli infection.

Hydroxyurea increases the production of Hgb F in patients with sickle cell anemia and thus ameliorates the disease clinically. The only successful therapeutic strategy so far for SCD is based on the use of hydroxyurea to increase the RBC content of Hgb F. Substantial reductions in pain rate, acute chest crises, and transfusion requirements have been achieved with hydroxyurea therapy. Long-term follow-up (9 years) of hydroxyurea-treated patients showed a 40% reduction in mortality with this therapy. The use of this agent in the ED is limited. Other interventions as described previously should be initiated earlier.

Novel therapies may include dipyridamole (Persantine), which has been shown to be a powerful inhibitor of the deoxygenation-induced fluxes of sickled cell polymerization, especially in dehydrated cells in vitro. However, more clinical trials are needed to demonstrate this benefit in vivo. Low-dose, longer-acting glucocorticoids, especially dexamethasone, have shown a benefit in the management of acute chest syndrome. However, more research is also needed. More recent studies and ongoing clinical trials have hypothesized that inhaled nitric oxide may be beneficial in managing various clinical conditions, including sickle cell anemia.

However, because the delivery of inhaled nitric oxide may have more limited applicability in the clinical setting as a result of inherent administration problems, the oral administration of L-arginine (precursor of nitric oxide) shows promise as a potential treatment for vasoocclusive crises and acute chest syndrome.

**DISPOSITION**

Patients with SCD who have uncomplicated painful crises and who receive hydration and adequate pain relief in the ED can be discharged. Adequate pain relief can be achieved on a variable basis for different patients, and no set rule exists about when this occurs. Some practitioners advocate for either temporal observation in the ED (6 hours) or a set amount of parenteral analgesics, most commonly opioids (two or three trials). Failure to achieve adequate pain relief requires inpatient admission (see the “Red Flags” box).

### RED FLAGS

**Indications for Hospital Admission**

- Inability to control pain
- Inability to maintain adequate hydration
- Acute chest syndrome
- Bacterial infection with unexplained fever, leukocytosis
- Cerebrovascular crisis (new neurologic sign or symptom)
- Priapism
- Splenic sequestration
- Aplastic or hemolytic crisis
- Acute abdomen, especially right upper quadrant syndrome
- Noncompliance with follow-up schedules
- Uncertain diagnosis

In the absence of contraindications (temperature > 38°C, respiratory signs or symptoms, low arterial oxygen saturation, tachycardia, or hypotension) and if adequate pain relief is attained, patients can be discharged home on a regimen of oral analgesics for 1 week, with continuity of care arranged. Patients who have minor infections can be discharged with oral antibiotics, more commonly amoxicillin-clavulanate, azithromycin, or levofloxacin. Primary care physicians should be contacted, and specialist care (hematology) referral should be arranged. Finally, counseling is indicated to prevent future crises, given the chronic nature of SCD. Preventive measures include advising the patient to adhere to an immunization schedule (especially pneumococcal, influenza, and hepatitis vaccines), to maintain biannual health care visits, and to take advantage of oral penicillin prophylaxis for patients with frequent infections.
**POLYCYTHEMIA VERA**

**EPIDEMIOLOGY**

PV is traditionally classified as a myeloproliferative disorder, which is a broad category of clonal stem cell diseases that include myelofibrosis with myeloid metaplasia and chronic myeloid leukemia. The true incidence and prevalence of PV are unknown. PV is relatively rare, occurring in 0.6 to 1.6 persons per million population. The disease has been recognized since the early twentieth century, and the initial description as presented by Osler has not changed. Fortunately, PV has the survival characteristics of a benign disease, and much still needs to be learned. For the EP, understanding the complications of the disease ultimately aids in its management.

**PATHOPHYSIOLOGY**

The Greek term *polycythemia* is synonymous with the word *erythrocytosis*, and it literally translates as “many cells in the blood.” *Absolute polycythemia* is a condition with increased RBC mass. Numerous primary and secondary polycythemic disorders lead to absolute polycythemia.

Primary and secondary polycythemias can be either acquired or congenital. Congenital polycythemias may result from inherited appropriate responses to tissue hypoxia, acquired conditions characterized by autonomous erythropoietin production (secondary polycythemias), defects in hypoxia sensing (either primary or secondary polycythemia), or inherited intrinsic defects in RBC precursors that render erythroid progenitors hypersensitive to erythropoietin (primary familial and congenital polycythemia).

PV, the most common primary polycythemia, is caused by the somatic change of a single hematopoietic stem cell, thus leading to clonal hematopoiesis. The molecular defects responsible for PV are unknown.

**PRESENTING SIGNS AND SYMPTOMS**

Symptoms of PV are related to hyperviscosity, sludging of blood flow, and thromboses, which lead to poor oxygen delivery and symptoms that include headache, dizziness (vertigo), tinnitus, visual disturbances, angina pectoris, and intermittent claudication. Hypertension is common in patients with PV.

Bleeding manifestations in PV involve primarily the skin and mucous membranes, findings suggesting defective primary hemostasis, and include ecchymosis, epistaxis, menorrhagia, and gingival hemorrhage. Gastrointestinal hemorrhage occurs less frequently but can be severe, necessitating hospitalization and blood transfusion, and it is often associated with the use of aspirin. This type of bleeding pattern is consistent with platelet defects (quantitative or qualitative) or von Willebrand disease.

Thrombosis, hemorrhage, and systolic hypertension result from the hyperviscosity associated with RBC mass expansion. Historically, thrombosis, both venous and arterial, occurred in up to 40% of patients during the course of the illness.

Dyspepsia and gastric or peptic ulceration appear to be more common in patients with PV than in the general population. The most serious complication other than thrombosis is pruritus.

Physical findings in PV are the result of manifestations of the myeloproliferative process and include splenomegaly (present in 75% of patients) and hepatomegaly (present in ~30% of patients). Plethora or a ruddy color results from the marked increase in total RBC mass. This manifests in the face, palms, nail beds, mucosa, and conjunctiva.

**DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC TESTING**

PV is a clinical diagnosis. Diagnostic tests are nonspecific, sometimes uninformative, and none of them establish clonality. The diagnosis is currently facilitated through the laboratory measurement of RBC mass, plasma volume, and arterial oxygen saturation and determination of oxygen pressure at 50% Hgb saturation. In the ED, elevated RBC counts and hematocrit values (including Hgb levels) are used to make this diagnosis. Generally, Hgb concentrations of at least 20 g/dL or hematocrit values of at least 60% in male patients and 56% in female patients can be presumed to indicate a myeloproliferative disorder. Direct measurement of the RBC mass should show an increase, with a normal or slightly decreased plasma volume. However, this nuclear medicine test uses radiochromium-labeled RBCs to measure actual RBC and plasma volume and is not readily available. If RBC mass results are available, the Polycythemia Vera Study Group diagnostic criteria can be used (Table 204.5).

The arterial oxygen saturation and carboxyhemoglobin levels are important to rule out hypoxia as a secondary cause of erythrocytosis.

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**Table 204.5** Polycythemia Vera Study Group Criteria for the Diagnosis of Polycythemia Vera

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Category A</th>
<th>Category B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total red blood cell mass</td>
<td>In male patients, ≥36 mL/kg; in female patients, ≥32 mL/kg</td>
<td>Thrombocytosis with a platelet count &gt;400,000/mL</td>
</tr>
<tr>
<td>Arterial oxygen saturation ≥ 92%</td>
<td>Splenomegaly</td>
<td>Leukocytosis with a white blood cell count &gt;12,000/mL</td>
</tr>
<tr>
<td>Serum vitamin B&lt;sub&gt;12&lt;/sub&gt; concentration &gt; 900 pg/mL</td>
<td></td>
<td>Leukocyte alkaline phosphatase &gt; 100 units/L</td>
</tr>
<tr>
<td>mEq or binding capacity &gt; 2200 pg/mL</td>
<td></td>
<td>Diagnosis</td>
</tr>
</tbody>
</table>

Diagnosis: A1 plus A2 plus A3
A1 plus A2 plus any two criteria from category B
TREATMENT

In the absence of other manifestations of disease, phlebotomy is the only therapy indicated for isolated erythrocytosis when the mechanism cannot be established. Phlebotomy can be initiated in the ED; however, a hematology consultation is required. Other agents such as aspirin, various antihistamines, synthetic androgens, and phototherapy have been described, and initiation of these therapeutic adjuncts can be carried out on an inpatient basis.

Finally, splenectomy is an option for patients with painful splenomegaly or repeated episodes of thrombosis that cause splenic infarction. At this juncture, inpatient evaluation is warranted, and surgical consultation should be obtained.

DISPOSITION

Patients requiring phlebotomy should be admitted. Bleeding and hemodynamically unstable patients require inpatient evaluation. In many patients with newly identified PV, drug administration and other interventions are not indicated in the ED setting. Asymptomatic patients can be referred to the hematologist for accurate determination of the underlying disease process, including measurements of RBC mass and karyotyping of bone marrow cells.

SUGGESTED READINGS


REFERENCES

References can be found on Expert Consult @ www.expertconsult.com.
REFERENCES


