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Anemia In The Emergency Department: Evaluation And Treatment

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CME Objectives

Upon completion of this article, you should be able to:

1. Differentiate between the 3 categories of anemia when considering a differential diagnosis.
2. Describe the diagnostic workup for patients presenting to the ED with anemia.
3. Summarize the general principles of transfusion therapy.

Prior to beginning this activity, see "Physician CME Information" on the back page.

Abstract

Anemia is a common worldwide problem that is associated with nonspecific complaints. The initial focus for the emergency evaluation of anemia is to determine whether the problem is acute or chronic. Acute anemia is most commonly associated with blood loss, and the patient is usually symptomatic. Chronic anemia is usually well tolerated and is often discovered coincidentally. Once diagnosed, the etiology of anemia can often be determined by applying a systematic approach to its evaluation. The severity of the anemia impacts clinical outcomes, particularly in critically ill patients; however, the specific threshold to transfuse is uncertain. Evaluation of the current literature and clinical guidelines does not settle this controversy, but it does help clarify that a restrictive transfusion strategy (ie, for patients with a hemoglobin < 6-8 g/dL) is associated with better outcomes than a more liberal transfusion strategy. Certain anemias may have well-defined treatment options (eg, sickle cell disease), but empiric use of nutritional supplements to treat anemia of uncertain etiology is discouraged.

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Case Presentations

A 54-year-old Hispanic male presents to the ED with the complaints of fatigue and weakness. The weakness is described as generalized, and the symptoms have been present and constant for the last 2 days. The patient denies hematemesis, hematochezia, dark-colored stools, hematuria, or other evidence of bleeding. He also denies chest or abdominal pain, dyspnea, diaphoresis, fever, or chills. The patient has not seen a doctor in the last 15 years and does not think he has any medical conditions. The only medication he has been taking is over-the-counter ibuprofen, which he has been taking daily since he injured his back at work 2 weeks ago. The patient works as a construction laborer and denies past surgeries or allergies. His vital signs are: blood pressure, 110/50 mm Hg; heart rate, 127 beats/min; respirations, 22 breaths/min; and SpO_2, 97% on room air. The patient is afebrile. His skin is warm and dry but, despite being dark-skinned, he appears a little pale. On eye examination, the sclerae appear to have a yellow hue. Cardiovascular examination reveals bounding pulses, a hyperdynamic precordium, and a grade II over VI soft, systolic murmur. The remainder of the examination is unremarkable, including a rectal examination, which is negative for occult blood. An ECG shows a sinus tachycardia but is otherwise normal. A basic chemistry panel is within normal limits; however, the CBC reveals a hemoglobin of 5.4 g/dL, hematocrit of 16%, WBC of 8000, and platelet count of 154,000. Based on the presenting symptoms and signs, the patient is likely to need RBC transfusions. An IV catheter is placed, and a normal saline infusion is initiated. A 500-mL bolus of normal saline reduces the heart rate to 105 beats/min. As you write the order for the transfusion, your nurse asks, "What is the goal for the transfusion and what is the cause of the anemia?" You think, "Good questions!"

In the next room, there is a 68-year-old male who reports 1 week of increasing weakness, dyspnea on exertion, and mild chest pressure. He states the reason for coming in today is that his chest pressure was substantially worse and was associated with diaphoresis. The patient has a history of atrial fibrillation (rate controlled) and has been taking dabigatran for the past 2 years. The patient denies hematemesis but has a history of dark stools. However, he states that he was placed on iron supplementation by his primary care physician over a year ago. He denies back pain, abdominal pain, fevers, chills, or focal neurological complaints. The patient has no known drug allergy and denies past surgeries, but he does have a history of hypertension and chronic anemia in addition to atrial fibrillation. Based on his chief complaints, an ECG, CBC, BMP, PT/INR, portable chest radiograph, and 325 mg of aspirin are ordered. His vital signs are: temperature, 37°C; blood pressure, 105/65 mm Hg; heart rate, 105 beats/min; respirations, 26 breaths/min; and SpO_2, 94% on room air. Overall, the patient's examination is unremarkable except for an irregularly irregular heart rate accompanied by a soft blowing systolic murmur, pale conjunctiva, and a positive fecal occult blood test on digital rectal examination. The patient's ECG is consistent with rate-controlled atrial fibrillation and shows ST-segment depression in the lateral leads. The CBC reveals a hemoglobin of 4.9 g/dL and a hematocrit of 15.2%, with a normal WBC and platelet count, PT, INR, and aPTT. His basic chemistry panel reveals an elevated BUN of 64 mg/dL and a creatinine of 2.3 mg/dL. The troponin is within the normal range. A normal saline bolus of 500 cc is administered. As you call cardiology, you wonder: what is the optimal treatment for this patient's presentation… cardiac catheterization or transfusion?

Just as you think you are getting control of the ED, a 6-month-old boy is brought in by his parents for congestion, increased work of breathing, and perioral cyanosis. The parents state that their child is taking longer to feed because he seems to be out of breath. This has been going on for several weeks, and they are unsure if their child has had a fever; they do not have a thermometer or a pediatrician. The patient was born at home with a midwife. The child's vital signs are: blood pressure, 70/50 mm Hg; heart rate, 155 beats/min; respiratory rate, 53 breaths/min; SpO_2, 92% on room air. He is afebrile. On your examination, the child is alert and responsive, but he is small for his age. He cries at appropriate aspects of the physical examination and is easily consoled by his mother. He is tachypneic with bilateral faint rales but does not demonstrate retractions or nasal flaring. The patient's face is dysmorphic. His skin has a yellow hue with scleral icterus and perioral cyanosis and acrocyanosis. On abdominal examination, he has significant hepatosplenomegaly. The rest of his physical exam is unremarkable. A basic chemistry panel is otherwise normal; however, his CBC reveals a hemoglobin of 7.8 g/dL, with a normal WBC and platelet count. The mean corpuscular volume is 75.4 fL, mean corpuscular hemoglobin concentration is 29.1%, and red cell distribution width is 16.2%. A chest radiograph is suggestive of pulmonary congestion. Pediatrics isn't your strength, and you wonder: why is this child anemic, and what are my next steps?

Introduction

Anemia is defined as an absolute decrease in the number of circulating red blood cells (RBCs). The diagnosis of anemia is based upon laboratory measurements of RBC indices that fall below accepted normal values. **(See Table 1.)** It is the most common

Table 1. Normal Values

Age	Hemoglobin (g/dL)	Hematocrit (%)	Red Blood Cell Count (x 10^6/mcL)
3 months	10.4-12.2	30-36	3.4-4.0
3-7 years	11.7-13.5	34-40	4.4-5.0
Adult man	14.0-18.0	40-52	4.4-5.9
Adult woman	12.0-16.0	35-47	3.8-5.2

hematologic disorder, and it is a global health problem. Worldwide, anemia affects 24.8% of the population and is more prevalent in children and pregnant women.[1] The prevalence of anemia varies depending on the RBC indices used to define it. In the Americas, anemia affects 29% of preschool children and 24% of pregnant women.[1] Another age group associated with an increased incidence of anemia is the elderly (defined as age ≥ 65 years). From a 2010 prospective population-based study of 8744 elderly individuals, the prevalence of anemia was 11%.[2]

Data on the frequency of anemia in the emergency department (ED) are less robust. Anemia occurs in 9% to 14% of pediatric ED patients and 14% of obstetric ED patients.[3-5] Data defining the frequency of its occurrence in the general ED population is lacking. In emergency medicine, anemia is divided into 2 broad categories: acute, with potential life-threatening complications; and chronic, with more stable clinical presentations. The focus of this issue of *Emergency Medicine Practice* is the ED evaluation of anemia and, more importantly, its management based on the best available evidence in the literature.

Critical Appraisal Of The Literature

A literature search of PubMed was performed using the search terms *anemia, transfusion, transfusion threshold,* and *emergency department.* Studies within the last 12 years were analyzed and included reviews, case reports, case series, and prospective randomized trials. More than 300 articles were reviewed, and 57 were selected for inclusion in this issue. In addition, data from the National Guideline Clearinghouse and the Cochrane Database of Systematic Reviews were used. The literature, much of it observational in form, shows that hemoglobin levels < 6 g/dL, especially in acute anemia, are associated with worse outcomes compared to individuals with hemoglobin levels above this value. On the other hand, the literature has also shown that the use of RBC transfusions is associated with poor outcomes. Randomized controlled studies show that using a restrictive transfusion strategy (defined as a transfusion hemoglobin threshold of < 6-8 g/dL) is associated with better outcomes than using a liberal strategy (defined as a transfusion hemoglobin threshold of < 9-10 g/dL). However, the hemoglobin level that should be the endpoint of transfusion therapy still has not been defined in the literature.

Etiology And Pathophysiology

The major function of the RBCs is to transport oxygen from the lungs to the tissues and transport carbon dioxide in the reverse direction. Oxygen transport is influenced by the amount of hemoglobin, its oxygen affinity, and blood flow. An alteration in any of the major components usually results in compensatory changes in the other 2 components. As an example, a decrease in hemoglobin is compensated by both inotropic and chronotropic cardiac changes that result in increased blood flow and a decreased hemoglobin affinity at the tissue level, thereby allowing the release of more oxygen. These compensatory responses may fail because of disease severity or underlying pathologic conditions. The result of failed compensatory responses is tissue hypoxia, cellular dysfunction, and eventual cell death.

Anemia often stimulates the compensatory mechanism of erythropoiesis controlled by the hormone erythropoietin. Erythropoietin is a glycoprotein produced primarily in the kidney. It regulates the production of RBCs by controlling differentiation of the committed erythroid stem cell. Erythropoietin is stimulated by tissue hypoxia and byproducts of RBC destruction. Erythropoietin levels are elevated in many types of chronic anemia.[6]

Bone marrow contains pluripotent stem cells that differentiate into erythroid, myeloid, megakaryocytic, and lymphoid progenitors. Erythropoietin stimulates the growth and differentiation of erythroid progenitors. When the normoblast extrudes its nucleus, it retains its ribosomal network, which identifies the reticulocyte. The reticulocyte will keep its ribosomal network for approximately 4 days, 3 of which are normally spent in the bone marrow and 1 in the peripheral circulation. The RBC develops as the reticulocyte loses its ribosomal network, and the mature RBC circulates for 110 to 120 days. The old erythrocytes are removed by macrophages that detect senescent signals. Under steady-state conditions, the rate of RBC production equals the rate of destruction. The mass of RBCs remains constant because an equal number of reticulocytes replace the destroyed senescent erythrocytes during the same period.[6]

Common sites of unrecognized blood loss from trauma include the pleural, peritoneal, pelvic, and retroperitoneal spaces. In addition to trauma, risk factors for blood loss include hereditary and acquired abnormalities to platelets and the coagulation system. This is especially true for the elderly, who are more likely to be taking anticoagulants and antiplatelet agents.[7,8] In nontraumatic situations of blood loss, the gastrointestinal tract, retroperitoneal space, peritoneal space, and pelvis must be considered.[9]

Causes other than blood loss may be responsible for severe anemia of rapid onset. Rare hemolytic conditions can cause rapid destruction of RBCs. **(See Table 2, page 4.)** More commonly, patients with chronic compensated hemolytic anemia (eg, sickle cell disease) have more stable anemias.

Beyond red cell production and destruction, the status of hemoglobin function must be considered. Impaired hemoglobin transport of oxygen is seen in

patients with carbon monoxide poisoning. Methemoglobinemia from nitrates, cyanohemoglobin from cyanide, and sulfhemoglobinemia resulting from hydrogen sulfide can severely decrease functional hemoglobin. These patients often present with symptoms associated with anemia, such as fatigue, altered mental status, shortness of breath, and other manifestations of hypoxia, but without signs of RBC loss or volume depletion.[10]

Differential Diagnosis

The differential diagnosis of anemia is facilitated by classifying the anemia into 1 of 3 groups: (1) blood loss, (2) decreased RBC production, or (3) increased RBC destruction. A complementary approach based on RBC morphology and indices is often used.[10] **(See the Clinical Pathway, page 8.)** Anemia secondary to acute blood loss is characterized by reduced hemoglobin value with normal RBC indices.

Decreased Red Blood Cell Production

Anemias caused by decreased RBC production have an insidious onset and are associated with a decreased reticulocyte count. The RBC indices and morphology manifested in a peripheral smear are useful in making the diagnosis. The definitive diagnosis is not usually made in the ED, and it may require bone marrow examination. In general, the emergency clinician does not initiate replacement therapy except in circumstances that require transfusion. Appropriate diagnostic tests may be ordered in the ED, but replacement of iron, vitamin B12, or folate without a definitive diagnosis should be avoided, especially the use of supplemental iron.

RBC indices are useful in classifying anemias caused by a production deficit. Their calculation formulas and normal ranges are provided in **Table 3**. Mean corpuscular volume (MCV) is a measure of RBC size. Decreases in MCV define microcytosis and increases reflect macrocytosis. Mean corpuscular hemoglobin (MCH) incorporates both RBC size and hemoglobin concentration. The MCH concentration is a measure of the concentration of hemoglobin. Low values represent hypochromia, whereas high values are noted in patients with decreased cell membrane relative to cell volume (such as spherocytosis). An additional index is the RBC distribution width (RDW), which is a measure of the homogeneity of the RBCs measured.[6,10]

Microcytic Anemias

Hypochromic microcytic anemias are subdivided into deficiencies of the 3 components of hemoglobin: (1) iron (iron-deficiency anemia), (2) globin (thalassemia), and (3) porphyrin (sideroblastic anemia and lead poisoning). Anemia of chronic disease, a secondary iron abnormality, is the last of the microcytic anemias. It must be remembered that not all microcytic anemias are the result of iron deficiency, and routine iron therapy for a patient with a low MCV and mean corpuscular hemoglobin concentration (MCHC) should be avoided.[10]

Iron-Deficiency Anemia

Iron deficiency is a frequent cause of chronic anemia seen in the ED, and it is usually occult in presentation. The diagnosis is made by laboratory evaluation of the fasting levels of serum iron, serum ferritin, and the total iron-binding capacity. Occult blood loss (especially gastrointestinal) may initially appear as iron-deficiency anemia. Therefore, a concentrated search for occult blood loss is vital.

Table 2. Common Causes Of Hemolysis

Extravascular Destruction

- Intrinsic Red Blood Cell Defects
  - Enzyme deficiencies (eg, glucose-6-phosphate dehydrogenase deficiency)
  - Hemoglobinopathies (eg, sickle cell disease, thalassemia)
  - Membrane defects (eg, elliptocytosis, hereditary spherocytosis)
- Extrinsic Red Blood Cell Defects
  - Autoimmune hemolytic anemia
  - Liver disease
  - Infections (eg, malaria, *Bartonella*)
  - Toxins (eg, nitrates, dapsone, aniline dyes, snake and spider bites)
  - Hypersplenism

Intravascular Destruction

- Transfusion reactions
- Microangiopathic trauma (eg, prosthetic heart valves, aortic stenosis, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation)
- Infection (eg, sepsis)
- Paroxysmal nocturnal hemoglobinuria
- Heat damage

Table 3. Red Blood Cell Indices

Index	Formula for Calculation	Normal Range
MCV	Hematocrit x 10/RBC count	81-100 fL
MCH	Hemoglobin x 10/RBC count	26-34 pg
MCHC	Hemoglobin x 100/hematocrit	31%-36%
RDW	Standard deviation of MCV/MCV x 100	11.5%-14.5%

Abbreviations: MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red blood cell distribution width.

Thalassemia

Thalassemia is a genetic autosomal defect associated with the decreased synthesis of globin chains. The hemoglobin molecule is present as 2 paired globin chains. Each type of hemoglobin is made up of different globins: normal adult hemoglobin is made up of 2 alpha chains and 2 beta chains ($alpha_2$ and $beta_2$), and fetal hemoglobin (HbF) is $alpha_2$ $gamma_2$. A separate autosomal gene controls the production of each globin chain. Decreased globin production in thalassemia results in a decreased hemoglobin synthesis and ineffective erythropoiesis. The ineffective erythropoiesis results in increased intramarrow hemolysis with destruction of RBCs before they are released.[6,10]

Homozygous beta-chain thalassemia (thalassemia major) occurs predominantly in populations of Mediterranean origins and represents one of the most common single-gene disorders. The disease is characterized by severe anemia, hepatosplenomegaly, jaundice, abnormal childhood development, and premature death. Patients are dependent on blood transfusions and often die from iron toxicity.[11,12]

Heterozygous beta-chain thalassemia (thalassemia minor) is manifested as a mild microcytic hypochromic anemia with associated target cells seen on the peripheral blood smear. These patients are usually asymptomatic, and no treatment is necessary.[6,10]

Sideroblastic Anemia

Sideroblastic anemia involves a defect in porphyrin synthesis and results in excess iron being deposited in the mitochondria of the RBC precursor. Defective heme synthesis results in ineffective erythropoiesis, mild to moderate anemia, and a dimorphic peripheral smear with hypochromic microcytes, along with normal and macrocytic cells. Sideroblastic anemia can be secondary to a rare sex-linked hereditary form, but it is more often a disease of the elderly. Pallor and splenomegaly may be noted, and the peripheral smear may demonstrate iron-containing inclusion bodies in RBCs. Idiopathic sideroblastic anemia is considered a preleukemic state, and acute myelogenous leukemia develops in approximately 5% of these patients. Secondary causes of sideroblastic anemia include toxins such as chloramphenicol, isoniazid, and cycloserine as well as diseases such as hemolytic and megaloblastic anemia, infection, carcinoma, leukemia, and rheumatoid arthritis. The exact mechanisms of these causative agents and diseases are unknown. Lead poisoning is one reversible cause of sideroblastic anemia. Elevated blood lead levels are diagnostic.

Anemia Of Chronic Disease

Anemia of chronic disease is common and is usually normochromic and normocytic. This form of anemia is characterized by low serum iron levels, low total iron-binding capacity, and normal or elevated ferritin levels. This anemia can be differentiated from iron deficiency by the total iron-binding capacity and the serum ferritin level. Because the hematocrit is seldom < 25% to 30%, these patients are often asymptomatic and therapy is not usually required. Any of several chronic comorbid disease states is the underlying cause of the anemia.[13]

Macrocytic Anemia

The most important cause of macrocytic anemia is the megaloblastic form. Megaloblastic anemia is the hematologic manifestation of a total-body alteration in DNA synthesis caused by a lack of vitamin B12 and folic acid. The deficiency affects tissues with rapid cell turnover, including hematopoietic cells and those of mucosal surfaces, particularly in the gastrointestinal tract. Hematopoietically, this deficiency is characterized by ineffective erythropoiesis and pancytopenia. The differentiation between folate and vitamin B12 deficiencies usually depends on measured serum levels.[6,10]

A unique feature of vitamin B12 deficiency is neurologic involvement. The classic neurologic complex includes loss of proprioception, weakness and spasticity of the lower extremities with altered reflexes, and variable mental changes. The latter 2 complaints may also be seen in folic acid deficiency.[6,10]

Macrocytic anemia is suggested when the MCV is > 100 fL. Large oval red cells (macro-ovalocytes) and hypersegmented polymorphonuclear neutrophils seen on the peripheral blood smear are believed to be diagnostic for megaloblastic anemias. Other useful laboratory tests include levels of vitamin B12, folate, red cell folate, and lactate dehydrogenase (LDH).[6,10] Liver disease, often associated with alcoholism, is the most common cause of macrocytic anemia. Macrocytic target cells may be seen on the peripheral smear in conjunction with this disorder. Hypothyroidism and hemolysis may also present as a macrocytic anemia.

Normochromic And Normocytic Anemias

The origin of normochromic and normocytic anemia secondary to decreased production is not as obvious as that of macrocytic and microcytic anemias. Since reticulocytes reflect RBC production in bone marrow, one hematologic parameter that can aid in the diagnosis of normocytic anemia associated with hypoproduction is the corrected reticulocyte count. Low reticulocyte counts reflect depressed bone marrow production. Normocytic anemia can be classified as being due to primary bone marrow involvement or a secondary marrow response to underlying disease. Aplastic anemia, myelophthisic anemia, and myelofibrosis are examples of normochromic and normocytic anemias.

Increased Red Blood Cell Destruction

The hemolytic anemias are defined by a shortened life span of the erythrocyte and can be acute or chronic in form. In their acute form, hemolytic anemias can be life-threatening and require rapid diagnosis and intervention. Fortunately, they are relatively rare compared to chronic hemolytic conditions. Chronic disorders may be related to primary blood disorders (eg, sickle cell anemia) or may be a result of other disease states (eg, chronic renal failure).

The clinical signs and symptoms of hemolytic anemia are caused by either intravascular or extravascular hemolysis. Intravascular hemolysis is usually associated with an acute and dramatic presentation. Large numbers of RBCs may be lysed within the circulation, and free hemoglobin initially binds to haptoglobin and hemopexin. These complexes are transported to the liver, converted to bilirubin, conjugated, and excreted. When the binding and transport system is overwhelmed, free hemoglobin may appear in the blood.[6,10]

The clinical appearance of intravascular hemolysis may vary from mild chronic anemia to prostration, fever, abdominal and back pain, and mental changes, as seen with transfusion reactions. Jaundice, brown to red urine, and oliguria induced by the hemoglobin complex can also occur.[6,10]

Extravascular hemolysis is more common and clinically better tolerated than intravascular hemolysis. Primary splenic overactivity, antibody-mediated changes, or RBC membrane abnormalities may cause normal splenic function to increase to pathologic levels. Hemolysis may also occur within the bone marrow.[14] The clinical picture of extravascular hemolysis is usually mild to moderate anemia, jaundice, and splenomegaly; however, the signs and symptoms vary with the severity and chronicity of the hemolysis. Because extravascular hemolysis is not associated with myoglobinuria or hemoglobinuria, the urine will appear normal in color or have an orange hue secondary to elevated bilirubin.

Sickle cell disease is the most common hemolytic anemia presenting to the ED. The emergency clinician should be familiar with this disease process. Even experienced physicians may overlook its major complications. Physicians with less experience may fail to recognize the complexity of this disease and the many potential complications.[15] For more information on managing patients with sickle cell disease, see the August 2011 issue of *Emergency Medicine Practice*, "Evidence-Based Management Of Sickle Cell Disease In The Emergency Department."

Extrinsic Alloantibodies

Alloantibodies are formed in response to foreign RBC antigens, and the ABO system is one of the most important RBC wall antigens. ABO incompatibility can be a life-threatening reaction. These antibodies are IgM in nature and, consequently, cause intravascular hemolysis.

Another set of antigens on the RBC is the Rh system. This system is unique in that individuals do not have antibodies that correspond to Rh antigens unless they have been sensitized by previous exposure to these antigens. The antibodies produced are IgG in nature and accelerate extravascular destruction of RBCs within the spleen and liver. Most autoimmune antibodies are directed toward antigens in the Rh system.

Extrinsic Autoantibodies

The major feature of autoimmune hemolysis is the production of an IgG or IgM antibody to an antigen present on the RBC membrane. Autoimmune hemolytic anemias are acquired disorders, with 40% to 50% being idiopathic. The remainder are associated with a number of diseases. **(See Table 2, page 4.)** Classification of autoimmune hemolytic anemias is based on the optimal temperature at which the antibody reacts with the RBC membrane. Therefore, there are warm-reacting (> 37°C) and cold-reacting (< 37°C) antibodies. The direct antiglobulin (Coombs) test helps differentiate the warm-reacting from the cold-reacting. The Coombs test is positive with warm-reacting antibodies and characterizes an autoimmune hemolytic anemia.[10,14]

Extrinsic Mechanical Causes

The peripheral blood smear may demonstrate schistocytes or fragmented RBCs, which should raise the suspicion of traumatic injury. Microangiopathic hemolytic anemia, cardiac trauma, and exercise-induced hemoglobinemia are the most commonly encountered forms of traumatic hemolysis. Microangiopathic hemolytic anemia is a form of microcirculatory fragmentation by fibrin deposited in the arterioles. It may be found in preeclampsia, vasculitis, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and vascular anomalies. The signs and symptoms are those of intravascular hemolysis, and treatment is directed at the underlying cause.

Increased cardiac blood turbulence can cause trauma to RBCs. It is most commonly found in patients with prosthetic valves but can also be associated with traumatic arteriovenous fistula, aortic stenosis, and other left-sided heart lesions.

March hemoglobinemia is a form of trauma caused by breaking of intravascular RBCs by repetitive pounding. Soldiers, marathon runners, and anyone with repetitive striking against a hard surface may incur this problem.[16]

Abnormal Sequestration

Hypersplenism can be caused by any disease that enlarges the spleen or stimulates the reticuloen-

dothelial system. The enlarged spleen traps blood components, which contributes to the splenomegaly. Splenic sequestration should be suspected in the setting of splenomegaly, pancytopenia, and marrow hyperactivity (elevated reticulocyte count).[6,10]

Prehospital Care

The role of emergency medical services (EMS) providers in the setting of anemia is limited. EMS is likely to be involved if the anemia is secondary to blood loss (particularly acute loss) or symptoms related to an underlying anemia. At times, the patient may already have a diagnosed anemia (such as sickle cell disease) and is presenting with an apparent complication of such. EMS providers can be particularly helpful in obtaining historical information, especially if the patient is unable to give an accurate history. Examples of key information from prehospital providers may include the presence of blood, coffee-ground emesis or an odor of digested blood at the scene, the presence of pill bottles at the scene (particularly antiplatelet or anticoagulant drugs), and the location or occupation of the patient (eg, an industrial site or site where chemical exposure is possible).[17]

Emergency Department Evaluation

Blood loss is the most common cause of clinically significant anemia.[1-4] The clinical manifestation of anemia depends on how rapidly the hematocrit decreases and on the patient's ability to compensate. Clinical signs and symptoms of blood loss potentially include tachycardia, hypotension, postural hypotension, and tachypnea. Complaints of thirst, light-headedness, syncope or near-syncope, weakness, altered mental status, and decreased urine output may also be present. Age, concomitant illness, and underlying hematologic, cerebral, and cardiovascular status tremendously influence the clinical findings. Children and young adults may tolerate significant blood loss with unaltered or minimally altered vital signs until a precipitant hypotensive episode occurs. Elderly patients commonly have underlying disease states that compromise their ability to compensate for blood loss.[18]

A history of trauma or clinical evidence of bleeding, such as hematochezia, hematemesis, hematuria, or menorrhagia, is often present. However, features less obvious to the patient (such as melena, history of peptic ulcer disease, chronic liver disease, or bleeding diathesis) should also be asked about. Antacids, H2 blockers, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants are medications that may suggest blood loss.

Patients presenting with chronic anemias often complain of fatigue and weakness. Other voiced complaints may include irritability, headache, postural dizziness, chest pain, decreased exercise tolerance, and dyspnea on exertion. When the anemia is of slow onset, the patient may adapt until the hemoglobin is very low, and they may have minimal complaints. The presence of easy bleeding may suggest a platelet or coagulation disorder. Jaundice, scleral icterus, or splenomegaly in the setting of anemia should alert the physician to the possibility of a hemolytic process. Neurologic symptoms (such as paresthesias, ataxia, or altered mental status) may suggest a megaloblastic anemia. A history about disorders known to be associated with anemia, such as renal failure, hepatic disease, hypothyroidism, and collagen vascular disease, should also be obtained.[18]

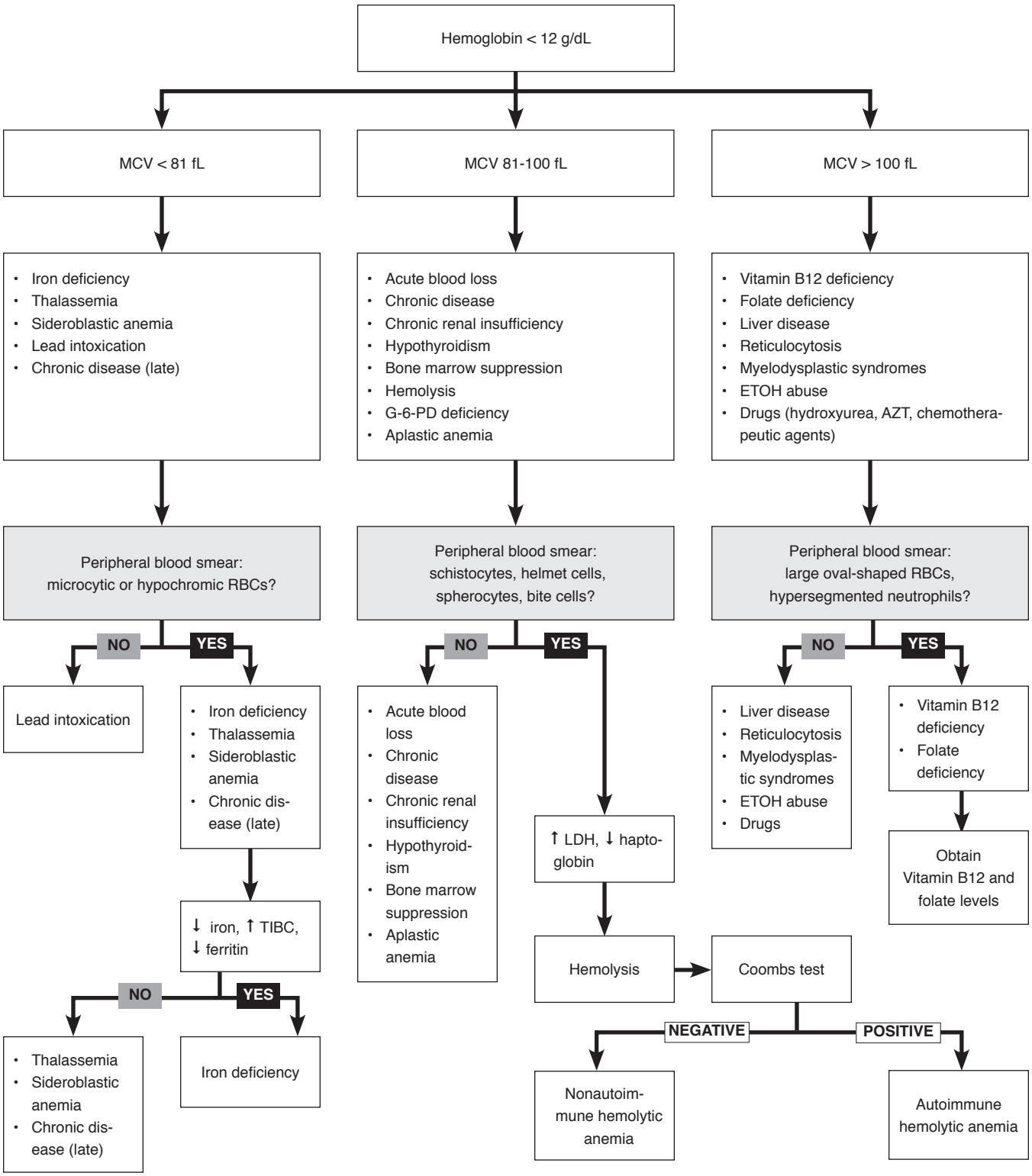
If anemia is suggested by the history, a thorough physical examination should be conducted. However, many patients with mild to moderate anemia will have a normal physical examination. The presence of tachycardia, bounding cardiac impulse, and functional systolic murmur may suggest a significant anemia. Pallor in the nail beds, face, palms, and conjunctivae is associated with significant anemia. Jaundice, splenomegaly, and scleral icterus are often seen in hemolytic anemias. Abnormal findings on neurologic examination may suggest folate or vitamin B12 deficiency. The presence of petechiae or ecchymosis suggests bleeding disorders that may have associated anemia. Generalized lymphadenopathy and hepatomegaly are also important physical findings that may be accompanied by anemia. Although physical findings are important, the ability to actually diagnose anemia based on physical examination is limited.[19-21]

Diagnostic Studies

As mentioned earlier, anemia is defined as an absolute decrease in the number of circulating RBCs, and it is a laboratory diagnosis based on an abnormally low value of hemoglobin, hematocrit, or RBC count. The hemoglobin measures the concentration of the major oxygen-carrying pigment in whole blood. The hematocrit is the percentage of a sample of whole blood that is occupied by intact RBCs. The RBC count is the number of RBCs contained in a specified volume of whole blood. Some institutions have the ability to determine the hematocrit at the bedside (ie, spun hematocrit). This can be useful for establishing the diagnosis of anemia but is not helpful in the evaluation of anemia. The evaluation of anemia generally follows one of two approaches: (1) the kinetic approach, which is based on the mechanism of the anemia; or (2) the morphological approach, which is based on RBC indices.

The more commonly used method of evaluation is the morphological approach. The RBC indices that are typically used are the MCV, MCH, MCHC,

Clinical Pathway For The Evaluation Of Anemia



Abbreviations: AZT, zidovudine; ETOH, ethanol; G-6-PD, glucose-6-phosphate dehydrogenase; Hgb, hemoglobin; LDH, lactate dehydrogenase; MCV, mean corpuscular value; RBC, red blood cell; TIBC, total iron-binding capacity.

and RDW. The MCV is calculated from the following formula: hematocrit x 10/RBC count. The MCV can be artificially elevated in the presence of cold agglutinins. The MCH is derived from the following formula: hemoglobin x 10/RBC count. Iron deficiency and thalassemias are the most common causes for a reduced MCH, and an elevated MCH denotes a macrocytosis of any cause. The MCHC is calculated by the following formula: hemoglobin x 100/hematocrit. Reductions in the MCHC are caused by the same conditions that will reduce the MCV and MCH. An elevated MCHC is almost always caused by the presence of spherocytosis or congenital hemolytic anemias (eg, sickle cell anemia).

The RDW is the least commonly used RBC index and represents a measure of the degree of variation in RBC size. The RDW is calculated from the following formula: standard deviation of MCV/MCV x 100. Elevated values indicate the presence of cells that differ in size. Although an abnormal RDW is not diagnostic for any particular disorder, elevated values indicate a need for a microscopic review of a manual peripheral blood smear.

With the current technology, all of the RBC indices are automated and derived at the same time the hemoglobin, hematocrit, and RBC count are measured. The evaluation of anemia is usually based on obtaining a complete blood count (CBC). Although the anemia is based on the RBC component of the CBC, the presence of abnormalities in the white blood cell count or platelet count may suggest causes for the anemia (eg, aplastic anemia, thrombotic thrombocytopenic purpura, or chronic lymphocytic leukemia).[6,10]

Additional laboratory studies may be indicated once the initial CBC and RBC indices are evaluated. **(See the Clinical Pathway, page 8.)** Some machines that measure the CBC will also report an automated evaluation of the peripheral blood smear. A peripheral blood smear is most useful in the evaluation of a hemolytic anemia, an anemia associated with thrombocytopenia, or white blood cell disorders. In these settings, a manual peripheral blood smear is indicated, which is more reliable than the automated form. In the presence of pancytopenia, a reticulocyte count should be considered. The reticulocyte count reflects the activity of the bone marrow. A decreased value in the setting of pancytopenia strongly suggests aplastic anemia. Iron studies, as well as other blood work, may be indicated but are not part of the initial evaluation of anemia.

Once anemia is diagnosed, the RBC indices should be evaluated, particularly the MCV. If the MCV is decreased (microcytic anemia), then serum iron, total iron-binding capacity, and ferritin values should be ordered. An elevated MCV is an indication for obtaining folate and vitamin B12 levels. In most ED settings, the results of these specialized blood tests will not be available while the patient is still in the ED. However, these data can be very useful to the healthcare provider that will be assuming care of the patient after the ED visit. An anemia with a normal MCV (particularly if hemolysis is considered) should prompt the ordering of a manual peripheral blood smear. The presence of schistocytes and helmet cells are often seen in microangiopathic (intravascular) hemolytic anemia. Spherocytes and elliptocytes are often seen in autoimmune hemolytic conditions, hereditary spherocytosis, and extravascular hemolysis. The peripheral blood smear associated with sickle cell disease (one of the most common extravascular hemolytic anemias) typically demonstrates sickle cells and target cells. A haptoglobin, LDH, and Coombs test should also be obtained if hemolysis is suggested. A positive Coombs tests is very suggestive of an autoimmune hemolytic anemia and will alter therapy.[6,10]

Treatment

As with any medical condition, assuring adequate oxygenation, ventilation, and hemodynamic stability are the primary priorities. Once the diagnosis of anemia is established, the next hurdle to overcome is to determine whether the anemia requires specific treatment, especially RBC transfusion. The universally accepted trigger for transfusion is based on the presence of clinical symptoms or signs that are determined to be caused by the anemia.

In an asymptomatic anemic patient, the need to transfuse is less clear and the literature is conflicting. In the past, the decision to transfuse RBCs was often based on the "10/30 rule," utilizing a threshold of hemoglobin of 10 g/dL or a hematocrit of 30% for transfusion.[22] In favor of a specific threshold to transfuse is the fact that anemia is associated with worse outcomes in some patients.[23,24] In a retrospective cohort study of 2083 patients, individuals with postoperative hemoglobin of 7.1 to 8 g/dL had 0% mortality and 9.4% morbidity, while patients with hemoglobin of 4.1 to 5 g/dL had 34.4% mortality and 57.7% morbidity.[25] However, arguing against transfusions based solely on a specific threshold are data from patients who refuse transfusion (usually for religious reasons). These patients can have similar or better outcomes than their transfused counterparts, despite having low hemoglobin values.[26,27] A 2009 retrospective cohort study, however, demonstrated that 1958 Jehovah's Witness patients had a 33.3% mortality rate when postoperative hemoglobin was ≤ 6 g/dL, which demonstrates that very low hemoglobin values (defined as a hemoglobin ≤ 6 g/dL) are not well tolerated.[28]

Transfusion of RBCs has its own set of problems. Besides the potential problems of transfusion reactions, infection, volume overload, iron overload

and transfusion-related acute lung injury, critically ill patients receiving RBC transfusions have worse outcomes.[29-31] In a recent study of 167 critically ill patients, transfusion was shown to be an independent risk factor for mortality, with an odds ratio (OR) of 2.67. In addition, transfused patients in this study had longer intensive care unit (ICU) and hospital stays.[32]

The optimal level of hemoglobin to trigger RBC transfusions in asymptomatic anemic patients is unknown.[32] Recent studies have attempted to better define indications for RBC transfusions. A Cochrane review of 6264 patients showed that a restrictive transfusion strategy (defined as a hemoglobin of 7-8 g/dL) was associated with a reduction in risk of receiving a RBC transfusion by 39%. The use of the restrictive strategy did not impact the rate of adverse events compared to a liberal transfusion strategy (defined as a threshold hemoglobin of 9.5-10 g/dL), and it was associated with a significant reduction in hospital mortality (relative risk of 0.77) but not a reduction in 30-day mortality.[33] The results of this Cochrane review are consistent with published clinical practice guidelines, which recommend using lower hemoglobin values (6-8 g/dL) as the threshold for RBC transfusion.[34-36] At this time, data are insufficient to use a threshold < 6 g/dL.[37]

Trauma and upper gastrointestinal hemorrhage are the most common indications for RBC transfusion in acute anemia.[38] A 2010 Cochrane review was unable to demonstrate a benefit from RBC transfusion in patients with acute upper gastrointestinal bleeding; however, the authors noted that the evidence at the time was suboptimal.[39] A recent study randomized 921 patients presenting with acute upper gastrointestinal bleeding to a restrictive transfusion strategy (hemoglobin < 7 g/dL) and a liberal transfusion strategy (hemoglobin < 9 g/dL). The 45-day mortality was 5% in the restrictive group and 9% in the liberal group ($P = .02$). The risk of rebleeding was also lower in the restrictive group (10%) compared to the liberal group (16%) ($P = .01$).[40] This study supports additional data from patients with acute bleeding that have shown that RBC transfusions increase the risk of rebleeding.[41] European guidelines for RBC transfusion for acute anemia recommend even lower thresholds (eg, hemoglobin < 6.4 g/dL in healthy adults aged < 60 years).[42]

Each unit of transfused packed RBCs in patients who are not actively bleeding increases the hemoglobin approximately 1 g/dL.[43] In a prospective study of 52 patients who were not bleeding, it was determined that post-transfusion hemoglobin levels can be reliably determined as little as 15 minutes after the transfusion is complete, and waiting a longer time to assess the effects of RBC transfusion is not required.[44]

The need to treat anemia in the setting of acute coronary syndromes is less clear. A retrospective study of 3324 elderly patients with acute myocardial infarction showed that RBC transfusion for hematocrit between 5% and 24% was associated with a reduction in 30-day mortality, (adjusted OR, 0.22).[45] In a cohort study of 39,922 patients, anemia was found in 30.6% of patients, but hemoglobin < 10 g/dL was seen in only 5.4% of patients. In this study, patients with ST-elevation myocardial infarction and a hemoglobin < 14 g/dL had higher mortality and recurrent cardiovascular events, with an adjusted OR of 1.21 ($P < .001$). Similarly, patients with non-ST-elevation myocardial infarction had high mortality and recurrent cardiovascular events with hemoglobin < 11 g/dL (OR, 1.31; $P = .027$).[46] In this same study, the rate of cardiovascular events and death increased with hemoglobin levels > 16 g/dL. However, a recent meta-analysis revealed an increase in all-cause mortality associated with RBC transfusions in patients with acute coronary syndromes compared to no transfusions: 18% versus 10.2%, respectively ($P < .001$). In this same study, a subgroup analysis showed that RBC transfusions may be of benefit in patients with hematocrit < 30%; however, the data were not strong enough to show statistical significance.[47] The practical application of this study is limited because the analysis was not stratified by baseline hemoglobin values. Since low hemoglobin levels are associated with worse outcomes in acute coronary syndromes and use of RBC transfusions may also be associated with worse outcomes, confusion remains as to which patients benefit, based on hemoglobin thresholds. Neither the American Heart Association nor the European Society of Cardiology specify a hemoglobin trigger to use in the setting of acute coronary syndromes.[48,49] Until better data are available, utilizing a hemoglobin < 9 to 10 g/dL to trigger the replacement of RBCs in this population seems prudent.

Autoimmune hemolytic anemia presents with its own particular issues. The treatment of choice for these patients is corticosteroids: 1 to 1.5 mg/kg of prednisone or its equivalent. However, improvement in the anemia associated with steroid therapy can take up to 1 to 3 weeks.[50] The threshold for RBC transfusion in these patients is even more confusing, since the use of incompatible blood can worsen the hemolytic process. Steroid therapy should be initiated in the ED; however, the use of RBC transfusion is best done in consultation with a hematologist. Despite these issues, a patient with acute autoimmune hemolytic anemia who has severe hemolysis should be approached the same as any patient with a life-threatening anemia, including the use of unmatched RBC transfusions, if indicated.

In the absence of a confirmed diagnosis for a specific form of anemia, the empiric use of iron, folate, and vitamin B12 supplements in the ED setting should be avoided. The use of nutritional supplements may delay the actual cause and workup of the anemia by assuming that the supplementation will remedy the problem.

Special Circumstances

The evaluation and treatment of anemia are the same for all age groups and patient populations. Certain forms of anemia (eg, sickle cell anemia) require specific therapies and transfusion thresholds that are beyond the scope of this article. Iron-deficiency anemia is the most common form of anemia in pregnancy.[51] A recent systematic review suggested benefit from oral iron replacement,[51] but there are no data supporting RBC transfusions for chronic anemia in this patient group.

The data supporting RBC transfusions for the treatment of anemia are less robust in children than in adults. However, the literature currently available shows similar thresholds and results as those used in adults. The TRIPICU study was a prospective randomized controlled trial of 648 critically ill children that compared a restrictive hemoglobin threshold for transfusion of 7 g/dL to a liberal threshold of 9.5 g/dL. There was no significant difference in morbidity or 28-day mortality between the 2 groups.[52] Another prospective randomized controlled study of 137 children with sepsis compared outcomes of transfusing for a hemoglobin < 7 g/dL to a hemoglobin < 9.5 g/dL. No clinically significant difference was noted in morbidity or ICU mortality.[53] A more recent systematic review concluded that patients with a hemoglobin > 7 g/dL do not have an outcome benefit from transfusions and suggested an increased risk of morbidity and mortality with transfusions.[54]

Controversies And Cutting Edge

The universally accepted indication for emergent RBC transfusion is hemorrhagic shock.[36-38] The decision to transfuse RBCs during the initial resuscitation in hemorrhagic shock is based on the clinical condition of the patient, the evidence of the amount of blood lost, and the potential for ongoing bleeding. The American College of Surgeons' Advanced Trauma Life Support (ATLS) course recommends considering RBC transfusions after administering 2 20-mL/kg fluid boluses of crystalloid solution in patients with ongoing hemorrhagic shock.[55] Despite the accepted principles of the ATLS course and the common-sense concept of blood transfusion in severe hemorrhage, there are little scientific data defining the goals for the use of RBC transfusions in the resuscitation of hemorrhagic shock.[35] The indications for emergency-release or uncrossmatched blood is even less well defined in the literature; however, the use of this type of RBC transfusion appears to be relatively safe.[56,57] For more information on the management of traumatic hemorrhagic shock, see the November 2011 issue of *Emergency Medicine Practice*, "Traumatic Hemorrhagic Shock: Advances In Fluid Management (Trauma CME)."

Disposition

Disposition of the patient with anemia is dependent on several factors. The patient who has symptoms related to anemia is likely to require admission to the hospital. In most cases, acute anemia will require admission, usually to an intensive care or acute care unit. The exception may be a case where the blood loss is known and well controlled (eg, a major laceration that has been repaired). A patient with acute anemia who is discharged needs explicit instructions on when to return or seek medical assistance. The vast majority of patients who require RBC transfusion will not be discharged from the ED unless the patient has been receiving chronic transfusions on an outpatient basis. Patients with asymptomatic stable chronic anemia can usually be safely discharged.[10] A stable, but new, anemia that is diagnosed in the ED should have follow-up arranged prior to discharge. Although specific laboratory tests that are indicated in the evaluation of anemia can be ordered in the ED, studies with delayed turnaround times can be followed up by the patient's physician or consultant.

Summary

Anemia is a common occurrence in all age groups. The initial focus of the emergency clinician evaluating anemia should be on determining whether the anemia is acute or chronic. Acute anemia is most commonly associated with blood loss, and chronic anemia is usually clinically stable. The clinical presentation of anemia is nonspecific and more commonly seen with acute anemia. The presence of jaundice or scleral icterus should alert the physician to the possibility of a hemolytic anemia.

The diagnosis of anemia is based on laboratory findings, and the evaluation for anemia should be based on a systematic approach. Iron deficiency is the most common cause of microcytic anemia, and if it is suspected, order serum iron, total iron-binding capacity, and ferritin levels. Suspicion of macrocytic anemia should prompt the ordering of folate and vitamin B12 levels. The results of studies ordered in the workup of microcytic or macrocytic anemias may not be available by the time disposition from the ED is being considered. A normocytic anemia or an elevated RDW should prompt the ordering of a peripheral blood smear, and the results can then be used to guide the ordering of additional laboratory studies.

The major dilemma associated with the evaluation of anemia is when to replace RBCs. The old "10/30 rule" should be avoided, since it is not supported in the literature. Patients can tolerate very low hemoglobin levels in chronic anemia; however, the literature shows that hemoglobin levels < 6 g/dL (especially in acute anemia) are

Risk Management Pitfalls For The Patient With Anemia

1. **"He didn't say he was on warfarin, so why would I check an INR?"**
   Many elderly patients are poor historians secondary to dementia or polypharmacy. In an elderly patient being evaluated for anemia, the INR should be considered, as elderly patients are more likely to omit mentioning prescribed medications than their younger counterparts and are more likely to develop coagulopathies from other causes.

2. **"Patients always exaggerate how much bleeding there is. Most is self-limited anyway."**
   Bleeding (eg, from the gastrointestinal tract and upper airway) can produce a significant amount of hemorrhage that may require admission to the hospital for observation.

3. **"The patient with a gastrointestinal bleed was old, but he didn't have any chest pain, so why would I get an ECG?"**
   Many older patients have major cardiovascular risk factors. With enough bleeding, there may be ECG changes to suggest cardiac ischemia secondary to supply/demand mismatch.

4. **"The hemoglobin was 9 g/dL, so I didn't think she needed a transfusion; I just gave her 1.5 L of normal saline for resuscitation."**
   By initiating too much crystalloid, there is the possibility of dilution of RBCs, causing decreased oxygen-carrying capacity and further injury (such as cardiac ischemia).

5. **"The patient came in with a history of moderate gastrointestinal bleeding and a blood pressure of 90/60 mm Hg. I gave him 2 L of crystalloid. The blood pressure improved, but the bleeding restarted."**
   While not true for every patient, it may be more advantageous to allow a patient to be mildly hypotensive as long as they do not show signs of tissue hypoperfusion. Increasing the blood pressure may disrupt primary hemostasis as hydrostatic forces within the blood vessels increase.

6. **"The vital signs are normal, so he can't be bleeding much."**
   Many patients are on beta blockers or other atrioventricular nodal blocking agents that may falsely normalize the vital signs in the face of significant hemodynamic compromise.

7. **"I gave the patient 4 units of packed RBCs, but she continued to bleed and deteriorate."**
   When patients bleed, they lose more than just RBCs. Coagulation factors and platelets are also lost as hemorrhage continues, and dilutional coagulopathies can occur. Resuscitation with fresh frozen plasma (and possibly platelets) may be required, depending on the degree of bleeding and amount of RBCs that are transfused.

8. **"Since the patient's hemoglobin was 11 g/dL with a low MCV of 78 fL, I figured the anemia was due to iron deficiency and I discharged him on iron supplements."**
   Although iron deficiency is the most common cause of a microcytic anemia, other causes of a low MCV need to be considered. As it turned out, this patient had thalassemia minor, which is usually asymptomatic and does not require treatment.

9. **"The hemoglobin was 9.8 g/dL; since it was < 10 g/dL, I transfused the patient."**
   No isolated threshold hemoglobin value has been shown to correlate with outcome of RBC transfusion. The use of blood transfusions should be based on whether the patient has clinical symptoms or signs suggesting a clinically significant anemia and not on as specific number.

10. **"The parents said there was blood in their baby's diaper, so I felt I needed to work up a potential coagulopathy and anemia."**
    In infants with a history of rectal bleeding, the first step is to confirm that what the parents saw was really blood. Even if blood is not confirmed on the rectal examination, a laboratory screening for anemia and coagulopathy should be pursued.

associated with worse outcomes compared to hemoglobin levels above this value. On the other hand, the literature has also shown that the use of transfusions is associated with poor outcomes. The unanswered question is, "At what point should a patient receive RBC replacement?" Current literature and clinical guidelines show that using a restrictive transfusion strategy (defined as a transfusion hemoglobin threshold < 6-8 g/dL) is associated with better outcomes than using a liberal strategy (hemoglobin < 9-10 g/dL). However, the hemoglobin level that should be the endpoint of transfusion therapy is still not known. A safe approach would seem to be to transfuse RBCs in asymptomatic anemia when the hemoglobin is < 6 to 8 g/dL but to limit transfusions once the hemoglobin is no more than 9 to 10 g/dL.

Disposition of the anemic patient is more straightforward. Patients with acute anemia and those requiring RBC transfusions are likely to need admission to the hospital. Patients with stable chronic anemia can usually be safely discharged from the ED, even if the laboratory workup is not complete. Unless it is an unusual circumstance, follow-up should be provided at the time of discharge.

Case Conclusions

In case 1, the RBC indices were normal (MCV = 86.7 fL, MCH = 27.3 pg, MCHC = 34.5%); however, the RDW was increased at 23.9%. Because the patient had scleral icterus and the RDW was elevated, a peripheral blood smear was ordered, which showed spherocytes. Based on the peripheral blood smear results, you were concerned for a hemolytic anemia and ordered LDH, haptoglobin levels, and a Coombs test. The LDH was elevated at 717 IU/L and the haptoglobin was reduced at 15 mg/dL. The Coombs test was positive, which confirmed the diagnosis of an acute autoimmune hemolytic anemia. Because RBC transfusion was anticipated but the patient had an acute autoimmune hemolytic anemia, you consulted hematology. Prednisone (1.5 mg/kg) was given and transfusion was also recommended with a goal of hemoglobin > 7 to 8 g/dL. The hematologist noted that there would likely be considerable delay in crossmatching blood for the patient. He recommended monitoring the hemoglobin and hematocrit every 3 to 4 hours, and if the patient became more anemic prior to receiving crossmatched blood, type-specific uncrossmatched blood should be transfused. The patient was admitted to the ICU in a stable condition, with a final diagnosis of acute autoimmune hemolytic anemia, likely caused by the ibuprofen.

In case 2, the patient was on dabigatran, so the administration of aspirin was not warranted and may have even been detrimental because of the concerns for gastrointestinal bleeding. In this case, his cardiac supply-demand mismatch was secondary to his acute blood loss and unlikely secondary to underlying coronary artery disease (though a contributing factor). Therefore, cardiac catheterization was not likely to benefit this patient. Correction of the patient's anemia would likely reverse the myocardial ischemia. The patient was transfused with 2 units of crossmatched packed RBCs. You did not give fresh frozen plasma or prothrombin complex concentrate because his coagulation studies were normal and he was not actively hemorrhaging. A repeat ECG showed normalization of the ST segments, and his symptoms dissipated. Both cardiology and gastroenterology were consulted, and the patient was admitted to the ICU. The final diagnosis was gastrointestinal bleeding from a gastric ulcer and myocardial ischemia secondary to supply-demand mismatch.

The child in the third case appeared to be in significant high-output heart failure. You treated him with supplemental oxygen and a 1 mg/kg dose of furosemide. You considered noninvasive positive pressure ventilation, but an appropriate face mask was not available for this very small patient. The scleral icterus and hepatosplenomegaly suggested a possible hemolytic anemia. In this case, further studies were warranted, including liver function tests, LDH, a blood smear, and a type and screen. The blood smear showed microcytic RBCs, tear drop cells, and target cells. An elevated LDH and decreased haptoglobin confirmed a hemolytic process. Liver function studies showed an abnormally high unconjugated bilirubin that correlated with his jaundice. Because of the hemolytic process and a microcytic anemia, you consulted hematology and ordered a hemoglobin electrophoresis. Based on the hematologic data, the hematologist suspected a thalassemia and recommended RBC transfusions to a hemoglobin of 9 to 10 g/dL and asked that the child be admitted to the ICU. Ultimately, this patient was found to have beta-thalassemia major and required additional transfusions and chelation therapy to reduce iron burden.

Time- And Cost-Effective Strategies

- A systematic approach to the evaluation of anemia can often determine the cause and limit the ordering of unneeded laboratory studies.
- The need for RBC transfusion should be based on clinical signs and symptoms and not on a specific hemoglobin level.
- The effectiveness of RBC transfusion can be determined within 15 minutes after administration (as opposed to hours).
- In the absence of a definitive diagnosis, prescribing iron, folate, or vitamin B12 supplementation in the ED should be avoided.
- Consider restricting transfusions to patients with a hemoglobin < 6 to 8 g/dL.
- Consider a restrictive transfusion approach in patients with a gastrointestinal bleed.

References

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

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

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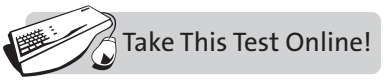
CME Questions



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1. A "restrictive" transfusion strategy:
a. Employs a hemoglobin threshold of < 9 to 10 g/dL
b. Employs a hemoglobin threshold of < 6 to 8 g/dL
c. Is associated with worse outcomes
d. Is the same as the 10/30 rule

2. Anemia of blood loss is characterized by a normal hemoglobin value with abnormal RBC indices.
a. True
b. False

3. Which of the following laboratory tests would help to differentiate between decreased RBC production and increased RBC destruction?
a. MCV
b. Reticulocyte count
c. Absolute hemoglobin difference
d. RDW

4. **What constellation of physical examination findings would you expect in a patient with extravascular hemolysis?**
   a. Scleral icterus, brown/red urine, splenomegaly
   b. Scleral icterus, normal or orange urine, splenomegaly
   c. Normal sclera, dark urine, no splenomegaly
   d. Normal sclera, normal urine, no splenomegaly

5. **In which of the following conditions would you least expect to find schistocytes on peripheral blood smear?**
   a. Mechanical prosthetic valve
   b. Thrombotic thrombocytopenic purpura
   c. Disseminated intravascular coagulation
   d. Sickle cell disease

6. **The most common cause of clinically significant anemia is:**
   a. Thalassemia
   b. Blood loss
   c. Liver disease
   d. Marathon running

7. **All factors being equal, which of the following hemoglobin levels would you not transfuse?**
   a. 4.5 g/dL
   b. 5.5 g/dL
   c. 10 g/dL
   d. 6.9 g/dL

8. **How much would you expect the hemoglobin to rise in a patient after being given 1 unit of packed RBCs?**
   a. 1 g/dL
   b. 2 g/dL
   c. 3 g/dL
   d. 4 g/dL

Physician CME Information

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

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