

# Anemia



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## KEYWORDS

• Anemia • Emergency Department • Evaluation • Management

## KEY POINTS

- Patients with anemia are frequently encountered in the emergency department, and emergency physicians often play an important role in the evaluation and management of anemia.
- After diagnosing anemia based on a low hemoglobin, hematocrit, or red blood cell (RBC) count, the RBC indices and peripheral smear should be evaluated.
- The initial treatment of anemia depends on the clinical status of patients.
- The decision to initiate blood transfusion is not always straightforward, and it is not a decision that should be taken lightly.

## INTRODUCTION

Patients with anemia are frequently encountered in the emergency department (ED), and emergency physicians (EPs) often play an important role in the evaluation and management of anemia. Some of these patients may have chief complaints directly related to their anemia, and others may be asymptomatic. Although many patients have findings consistent with anemia on routine laboratory tests, only a small percentage will require acute intervention. An understanding of the broader types of anemia as well as how to manage such patients is important in the day-to-day practice of an EP, as the presence of anemia will impact treatment plans for a wide variety of other disorders. This article reviews the evaluation and management of adult patients presenting to the ED with anemia.

## BACKGROUND

### *Definition*

Anemia is defined as a condition in which the body has a decreased amount of circulating erythrocytes, or red blood cells (RBCs). It can also be defined as a decreased hemoglobin concentration or RBC mass compared with age-matched controls.<sup>1</sup> As

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with almost all human laboratory assays, *normal value* is a statistical term used to define a range within which 95% of the population's values fall.<sup>2</sup> The World Health Organization (WHO) defines anemia as a hemoglobin less than 13 g/dL in adult men and less than 12 g/dL in non-pregnant adult women.<sup>3</sup> However, these values were chosen somewhat arbitrarily; most laboratories define anemia as the lowest 2.5% of the distribution of hemoglobin values from a normal, healthy population.<sup>4</sup>

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## **Anatomy**

### **Erythropoiesis**

*Erythrocytes* originate in the bone marrow as hematopoietic progenitor and precursor cells. After several cell divisions, mature RBCs emerge as discoid, pliable anucleate cells, each containing 4 hemoglobin molecules. An erythrocyte typically survives for 100 to 120 days before undergoing apoptosis (programmed cell death).<sup>5</sup> Erythropoiesis, or the process of RBC production, occurs in a regulated fashion under the control of the hormone erythropoietin (EPO). EPO is a glycoprotein, secreted from peritubular cells within the kidney when renal cells detect decreased oxygen in circulation available for metabolism.<sup>1,6</sup> Successful erythropoiesis depends on 4 factors: a stimulus for erythrocyte production, the ability of precursor cells in the bone marrow to respond to the stimulus, the presence of essential nutrients required for erythrocyte synthesis, and the life span of the erythrocyte.<sup>7</sup>

Erythropoiesis should be stimulated in response to most forms of anemia, but it takes 3 to 7 days for new RBCs to appear in the blood.<sup>5</sup>

### **Hemoglobin**

*Hemoglobin* is a tetramer made up of 2 pairs of polypeptide (globin) chains, with each chain containing an iron-containing heme complex for oxygen binding. The structure of hemoglobin is under both genetic and environmental influence.<sup>4</sup>

Various forms of hemoglobin are known to exist. In adults, hemoglobin A and A2 are the major and minor forms of hemoglobin, respectively. Hemoglobin F, present in utero, should make up less than 1% to 2% of adult circulating hemoglobin but may be present in higher quantities in the setting of other hemoglobin variants.

Under genetic influence, other forms of hemoglobin may make up the minority or most of the circulating hemoglobin, affecting the overall RBC oxygen-carrying capacity. Hemoglobin S is the predominant hemoglobin in sickle cell disease. Other hemoglobin variants also include hemoglobin C and E as well as thalassemia.<sup>4</sup> Hemoglobin variants generally have altered oxygen affinity, a shorter life span, and are more unstable leading to increased hemolysis.

### **Production abnormalities**

Abnormalities in the production of erythrocytes can be caused by insufficient cofactors, such as vitamin B12 and folate, or can be caused by genetic abnormalities, such as congenital hemoglobinopathies or membranopathies. *Hemoglobinopathies* are abnormalities within the globin chains, as described earlier. *Membranopathies* are abnormalities in the membrane of the RBC; hereditary spherocytosis and elliptocytosis are 2 examples.

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## **Cause**

### **Acute anemia**

Anemia can be classified in several different ways. For the EP, the most important initial questions for classification is whether the anemia is acute or chronic. This classification can be identified based on clinical presentation as well as laboratory investigations. In the ED, the common causes of acute anemia include hemorrhage

secondary to trauma, gastrointestinal (GI) blood loss, ruptured aneurysm, or genitourinary bleeding including postpartum hemorrhage and ruptured ectopic pregnancy. Less often, rapid hemolysis from aplastic crisis or acute splenic sequestration in sickle cell disease can be a cause of acute anemia. Even more rare, but still seen in the ED, are the autoimmune hemolytic anemias and disseminated intravascular coagulation (DIC).

### **Chronic anemia**

If the anemia is not caused by acute RBC loss, it can be characterized by its cause: (1) destruction of RBCs or (2) decreased production of RBCs. A concomitant approach using RBC size (mean corpuscular volume [MCV]) can help further describe the anemia (**Tables 1** and **2**).

The most common type of anemia is iron deficiency anemia, followed by anemia of chronic disease in the older adult population. A significant percentage of those with iron deficiency anemia are found to have a GI source of bleeding.<sup>11</sup>

### **Epidemiology**

Statistical and epidemiologic data on anemia are surprisingly limited because of varying definitions as well as the division of various population groups (ie, male, female, infants, pregnant women, and so forth). However, the best estimate for the prevalence of anemia comes from WHO data from 1993 to 2005. The results estimate that anemia affects approximately 24.8% of the population, globally, with the highest percentages seen in preschool-aged children, pregnant women, and the elderly, respectively.<sup>12</sup>

In the United States, the prevalence estimate decreases to less than 5% of the population, with the same groups (preschool, pregnancy, elderly) affected more significantly. In those older than 65 years, the prevalence of anemia climbs to 11%<sup>13</sup> and increases to more than 30% in those older than 85 years.<sup>11</sup> Although common in the elderly, anemia should not be considered a normal part of aging.<sup>8,14–16</sup> In older adults, the risk factors for anemia include male sex, increased age, nutritional deficiencies, and chronic disease.<sup>17,18</sup>

In pregnancy, more than 50% of women in underdeveloped or developing nations will develop anemia. In developed nations, this rate decreases to 20%.<sup>19</sup> In the United States, the biggest risk factor for developing anemia in pregnancy is low socioeconomic status; nutritional deficiencies and chronic disease also contribute.

In general, women have lower hemoglobin levels than men. African Americans also have a lower hemoglobin concentration that is partly caused by the increased prevalence of hemoglobin variants.<sup>20</sup>

**Table 1**

**Anemia characterized by destruction and decreased production of RBCs**

<b>Destruction/Loss</b>	<b>Decreased Production</b>
Intrinsic hemolysis: spherocytosis, elliptocytosis, sickle cell, pyruvate kinase deficiency, G6PD deficiency	Abnormal hemoglobin synthesis: iron deficiency, thalassemia, anemia of chronic disease, megaloblastic
Extrinsic hemolysis: immune, microangiopathic, infectious, hypersplenism	Hematopoietic stem cell lesions: aplastic anemia, leukemia Bone marrow infiltration: lymphoma, carcinoma Immune mediated: aplastic anemia, pure red cell aplasia

*Abbreviation:* G6PD, Glucose-6-phosphate dehydrogenase.

Table 2 Typical causes of chronic anemia	
Microcytic (MCV<80)	Iron deficiency Thalassemia Anemia of chronic disease (eg, rheumatoid arthritis, congestive heart failure, chronic renal failure) Sideroblastic anemia Lead poisoning
Normocytic	Kidney disease Hemolytic anemia (spherocytosis, elliptocytosis, sickle cell disease, G6PD) Nonthyroid endocrine gland failure Autoimmune (drug, viral, idiopathic) Microangiopathic Infection (malaria, parvovirus) Mild form of most acquired forms of anemia
Macrocytic (MCV>100)	Megaloblastic Vitamin B12 deficiency Folate deficiency DNA synthesis inhibitors (nonmegaloblastic) Myelodysplasia Liver disease Reticulocytosis Hypothyroidism Bone marrow failure states (ie, aplastic anemia)

Abbreviation: G6PD, Glucose-6-phosphate dehydrogenase.  
Data from Refs. <sup>8-10</sup>

CLINICAL PRESENTATION

History and Physical Examination, Signs and Symptoms

Anemia can present anywhere on a grand spectrum of signs and symptoms: from the vague and nonspecific symptoms of a slowly developing anemia to the hemorrhagic shock of acute blood loss. After the initial stabilization and resuscitation, a thorough history and physical examination should be performed to help confirm the presence of anemia and to identify the potential underlying causes of anemia.

History

Patients with documented anemia should be questioned regarding obvious blood loss from 3 common sources in acute or chronic anemia: the GI tract, genitourinary tract, or pulmonary systems.<sup>4</sup> Additionally, for women, a menstrual history should be obtained. Specifically, patients should be asked about hematemesis, hematochezia, melena, and heavy menstrual bleeding. These types of blood loss, as well as blood loss secondary to trauma, are commonly reported by patients as a primary concern in their initial presentation.

Hematuria, either microscopic or macroscopic, can point toward a direct source of bleeding or may suggest underlying renal disease, which may be affecting erythropoiesis. Finally, hemoptysis may be obvious; or in some cases, patients may not have noticed blood in any sputum because of swallowing of sputum.

Other key aspects of the patient history include the past medical history, recent procedures or surgeries, medications, a brief dietary history, and family history relevant to anemia. The *past medical history* may reveal a chronic disease that has the potential to cause anemia, such as rheumatoid arthritis, renal disease, or congestive heart failure.

*Recent surgeries or procedures* may be the direct cause of anemia; or patients may be having secondary bleeding, such as a retroperitoneal hemorrhage after a cardiac catheterization. *Medications* that may contribute to anemia come from several different classes: nonsteroidal antiinflammatories including aspirin, bisphosphonates, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, anticonvulsants (particularly phenytoin and carbamazepine), cephalosporins and sulfa drugs, and certain chemotherapeutics.<sup>21–24</sup> The *dietary history* may reveal an obvious dietary source of anemia, such as folate or B12 deficiency. A *family history* may reveal potential inherited anemias, such as sickle cell disease or hereditary spherocytosis; these anemias are usually detected in childhood but occasionally may not present until adulthood.

### **Signs and symptoms**

Many patients will present to the ED with the diagnosis of anemia noted on routine blood work performed as an outpatient or on preoperative tests. Most of these patients are completely asymptomatic, as the anemia has developed over weeks to months and the body has effectively compensated for a lower oxygen-carrying capacity state.

Other patients with anemia may present to the ED with vague symptoms, such as fatigue, weakness, thirst, listlessness, lightheadedness or dizziness, chest pain, dyspnea, and decreased exercise tolerance. In the elderly, increased falls, impaired cognition, and general physical decline may also occur.<sup>14</sup> More significant or more precipitous anemia can lead to syncope or near syncope and vital sign abnormalities, including hypotension, tachycardia, and tachypnea.

The initial signs and symptoms of anemia are caused by tissue hypoxia and physiologic compensatory mechanisms. Because oxygen-carrying capacity normally exceeds oxygen needs by a factor of 4 while at rest, hemoglobin levels may decrease significantly before patients exhibit any signs or symptoms of anemia.<sup>25</sup> There is no specific hemoglobin concentration that elicits symptoms; however, most adult patients will report symptoms once hemoglobin levels decrease to less than 7 g/dL.<sup>26,27</sup> Patients who have chronic anemia or congenital forms of anemia (ie, sickle cell disease, hereditary spherocytosis) may not report symptoms until the hemoglobin decreases to less than 5 g/dL.<sup>28</sup>

Most patients presenting to the ED with anemia will have a normal physical examination. However, certain findings may direct the EP to a cause. On physical examination, pallor, jaundice, or scleral icterus may suggest a hemolytic anemia. Signs of the underlying cause may also include thyromegaly, lymphadenopathy, cardiac murmurs, crackles on pulmonary auscultation, hepatomegaly or splenomegaly, palpable mass, abdominal distension with a fluid wave, abdominal tenderness, joint swellings or deformities, rashes or petechiae, and melena or blood on digital rectal examination. A search for traumatic injuries should also be completed.

### **Acute blood loss**

The normal physiologic response to acute blood loss includes increased myocardial contractility, increased vascular tone, and increased sympathetic outflow to help conserve physiologic functions until the circulating plasma volume is restored. These reflexes appear in stages depending on the amount of volume lost. The physiologic changes that occur in this response do so in order to maintain oxygen delivery to the tissues, particularly the brain and heart.<sup>29</sup> Initially, this can appear as orthostatic hypotension, increased diastolic blood pressure, and tachycardia.<sup>25</sup> If the circulating plasma volume continues to decrease, such as in large-volume acute blood loss, hypotension will occur.

Diagnostic Studies

Complete blood count

A complete blood count (CBC) is needed to make the initial diagnosis of anemia. The hemoglobin, hematocrit, or RBC value may be used to confirm the diagnosis, although the hemoglobin value is the most accurate. Hemoglobin levels are usually directly measured by spectrophotometric (co-oximetry) analysis, and the hematocrit is then calculated from this result. The typical calculation is an approximate 3-fold conversion from hemoglobin to hematocrit levels; however, this relies on a normal mean cell hemoglobin concentration.<sup>30</sup> Point-of-care methods of testing use the method of conductivity to measure the hematocrit and then calculate the hemoglobin value. However, accurate results depend on physiologically normal patients; results become more inaccurate at a hematocrit value of less than 30%.<sup>22</sup> These tests also tend to underestimate hematocrit values in general.<sup>31</sup>

The CBC also includes various RBC indices that can help determine the cause of the anemia present. This subject is covered in detail in the “*Differential Diagnosis (Morphologic Approach)*” section. Normal values will vary slightly, based on individual laboratories; but estimates for these laboratory values for adult men and women are listed in [Table 3](#).

The red cell distribution width (RDW) is a measure of RBC variation in size. A low value indicates a more homogenous sample, but this does not mean the cells are of normal size.

The MCV refers to how much space the RBCs take up within the plasma. The MCV is calculated by dividing the hematocrit by the RBC count. Microcytic refers to a low MCV, and macrocytic refers to a high MCV.

The mean cell hemoglobin (MCH) is calculated as the hemoglobin divided by the RBC count. Similar to the MCV, hypochromic (low MCH) and hyperchromic (high MCH) anemias have distinct causes.

Finally, the MCH concentration (MCHC) is the hemoglobin divided by the hematocrit, indicating the average concentration of hemoglobin within the RBCs.

Peripheral smear

A peripheral blood smear may be triggered on an automated CBC if abnormal cells are detected. Otherwise, if there is particular concern for a specific diagnosis, a peripheral smear should be ordered; this can be helpful to look at the shape of the RBC as well as abnormal circulating cells ([Table 4](#)).<sup>4</sup>

Table 3 Normal RBC values in females and males		
Parameter	Normal Values (Male)	Normal Values (Female)
RBC	5.2	4.6
Hemoglobin	15.5	14.0
Hematocrit	47	41
MCV	90	90
MCH	30	30
MCHC	34	34

Abbreviations: MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; RDW, red cell distribution width.

Data from Marks PW. Approach to anemia in the adult and child. In: HoffmanR, Benz EJ, Silberten LE, et al, editors. Hematology: basic principles and practice. 6th edition. Philadelphia: Elsevier; 2013.

**Table 4**  
**Peripheral smear findings and their associated disease states**

<b>Abnormal Cell Findings in the Peripheral Blood Smear</b>	<b>Associated Disease State</b>
Schistocytes	Hemolysis, microangiopathic hemolytic anemia
Spherocytes	Hereditary spherocytosis, autoimmune hemolytic anemia
Sickle cells	Sickle cell disease
Burr cells	Microangiopathic hemolytic anemia, chronic renal failure
Codocytes or target cells	Hemoglobinopathies, iron deficiency anemia
Dacryocytes or teardrop cells	Leukoerythroblastic syndrome
Rouleaux formation	Waldenström macroglobulinemia, multiple myeloma, inflammatory states
Clumping	Cold antibodies

From this list, the most relevant results to the EP are the findings of schistocytes, which can be associated with thrombotic microangiopathies, such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), or sickle cells in rarely undiagnosed patients with sickle cell.

#### **Other laboratory tests**

There are very few other tests relevant to making the diagnosis of anemia within the ED. In certain circumstances, additional testing may guide the treatment plan. When anemia is diagnosed or suspected in patients with sickle cell anemia in acute crisis, the reticulocyte count is a useful marker of appropriate marrow response. Reticulocytes are immature RBCs. If elevated levels of reticulocytes are detected within the serum (>1.5% in men, 2.5% in women), accelerated RBC production is occurring within the marrow. In the setting of a normal hemoglobin, an elevated reticulocyte count is an abnormal finding and suggests a diagnosis of polycythemia vera. In the setting of anemia, the reticulocyte index should be calculated to determine if the marrow response is adequate. The reticulocyte index is calculated as follows: [reticulocyte count (%)  $\times$  (patient's hematocrit/normal hematocrit)]/2. An index greater than 2 suggests an appropriate response.

Further clues to the cause of anemia can be obtained by looking at the bilirubin level as well as the blood urea nitrogen (BUN) and creatinine levels. Indirect bilirubin levels can increase in the setting of hemolytic anemia. An elevated BUN level can be present because of the hemoglobin being absorbed from the gut in a slow GI bleed. An elevated creatinine suggests kidney disease, which can also be a cause of anemia caused by underproduction of EPO.<sup>10</sup>

Hematologists may request that further tests be performed to assist in diagnosis. These tests should ideally be done before blood transfusion. These tests include the haptoglobin, lactate dehydrogenase (LDH), and Coombs test, among others.

Haptoglobin is an acute phase reactant that is present with hemolysis and has a half-life of 5 days. It binds to the protein portion of free hemoglobin. When binding occurs, the complex is rapidly cleared from the serum; low serum levels of haptoglobin (normal 36–195 mg/dL) indicate hemolysis.<sup>32</sup>

LDH is released into the circulation during erythrocyte destruction and hemolysis.<sup>21</sup> This enzyme will be elevated in hemolytic anemia.

The Coombs tests consist of the direct antiglobulin test (DAT) and the indirect antiglobulin test. A positive DAT indicates the presence of antibodies on the erythrocyte membrane, which can indicate autoimmune hemolytic anemia.<sup>21</sup>

If the diagnosis of microcytic anemia is made or if, in the elderly, there is suspicion of iron deficiency anemia, then further laboratory tests should be sent before blood transfusion. Obtaining *iron studies* typically refers to 4 separate assays that, when analyzed together, can help determine the underlying cause of the microcytic anemia. These 4 assays include serum iron level, ferritin, transferrin, and total iron binding capacity. The interpretation of these values is discussed further later.

Finally, if the anemia is macrocytic (elevated MCV) or is present in the elderly and normocytic, vitamin B12 and folate levels should be evaluated.

### ***Differential Diagnosis (Morphologic Approach)***

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After diagnosing anemia based on a low hemoglobin, hematocrit, or RBC count, the RBC indices and peripheral smear should be evaluated. In addition, the reticulocyte index should be calculated. If the peripheral smear is available and abnormalities are identified, this can provide essential first clues as to what type of anemia may be present ([Fig. 1](#)).

If the reticulocyte index is greater than or equal to 2, then there is an appropriate marrow response. This result suggests blood loss or RBC destruction. If the index is less than 2, there is an inappropriate marrow response to the anemia and the RBC indices are then useful.<sup>8</sup>

The first RBC index to evaluate is the MCV. This evaluation will determine if the anemia is microcytic (MCV<80), normocytic, or macrocytic (MCV>100).

#### ***Microcytic anemia***

Once a microcytic anemia is identified, further testing should be conducted to determine if the anemia is caused by iron deficiency, thalassemia, or anemia of chronic disease. In addition, iron studies can help differentiate between the 3 causes. The differential diagnosis of microcytic anemia is shown in [Table 5](#).

Starting with the ferritin level is perhaps the simplest way to differentiate iron deficiency anemia from other causes of microcytic anemia. A low serum ferritin is the most reliable indicator of iron deficiency anemia, and a level less than 15 mg/L is 99% specific.<sup>8,33</sup> If the serum ferritin is normal or high, the anemia can be caused by alpha or beta thalassemia minor or anemia of chronic disease. If previous CBCs are available and it is noted that patients consistently have a low MCV, then the anemia is more likely congenital, and thalassemia is more likely.

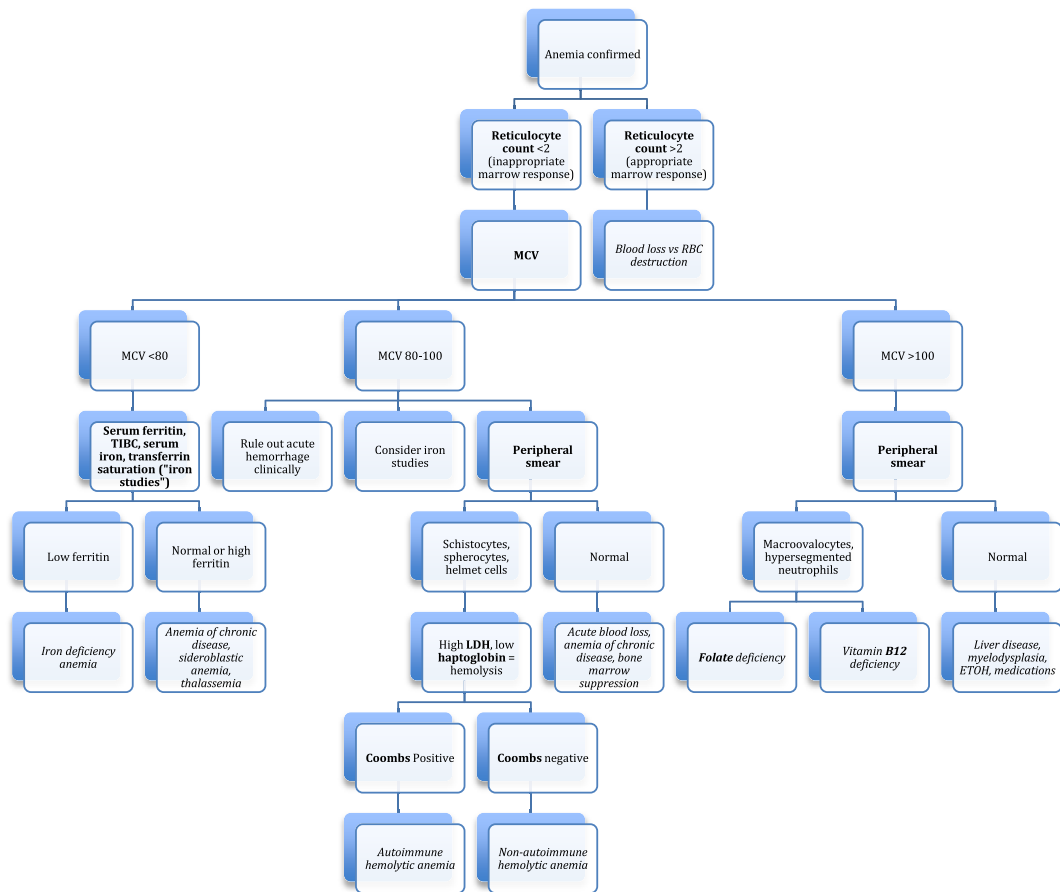
Note that anemia of chronic disease can be microcytic or normocytic. The classic findings are listed in [Table 2](#). One rare type of anemia that can present very similarly to anemia of chronic disease is sideroblastic anemia, which is an anemia caused by bone marrow disorder. This anemia can be acquired or hereditary, and a high RDW suggests the diagnosis.<sup>5</sup>

#### ***Normocytic anemia***

The finding of normocytic anemia should trigger a search for readily treatable causes. The reticulocyte count can be useful in determining the underlying cause of normocytic anemia. If the reticulocyte count is normal, then forms of anemia typically classified as microcytic or macrocytic may be present. If the reticulocyte count is high in the setting of normocytic anemia, then a Coombs test will help further differentiate a cause.

The RDW is the next helpful index to further classify the anemia. If the RDW is normal, then anemia of chronic disease or caused by renal failure is suggested; renal insufficiency with a creatinine as low as 1.5 mg/dL may cause anemia.





**Fig. 1.** Differential diagnosis of anemia flow diagram. ETOH, alcohol; TIBC, total iron binding capacity. Items listed in bold indicate laboratory investigation; items listed in italics indicate likely diagnosis.

Table 5 Microcytic anemia								
	RBC	Hb	MCV	MCHC	RDW	Iron	Ferritin	TIBC
Iron deficiency	Low	Low	Low	Low	High	Low	Low	High
Thalassemia	Normal or high	Low	Very low	Low	Low	Normal	Normal	Normal
Chronic disease	Normal or low	Low	Low or normal	Normal	Low	Low	Normal	Low

Abbreviations: Hb, hemoglobin; TIBC, total iron binding capacity.  
Data from Refs.<sup>2,9,17</sup>

Hemolytic anemia is a common cause of normocytic anemia and, for the EP, is potentially one of the most serious and time-sensitive forms of anemia. This disorder is suggested by increased indirect bilirubin and schistocytes seen on peripheral smear. If hemolytic anemia is suspected, a decreased haptoglobin and increased LDH and reticulocyte count will further support the diagnosis. DIC, TTP, HUS, and hemolysis associated with preeclampsia or eclampsia are all forms of hemolytic anemia that have high morbidity and mortality. A positive Coombs test suggests an autoimmune cause, whereas a negative Coombs test suggests a congenital form of anemia (membranopathies, enzymopathies, or hemoglobinopathies) or microangiopathic hemolysis.

**Macrocytic anemia**

Macrocytic anemia, with an MCV greater than 100, can be divided into megaloblastic and nonmegaloblastic anemias. Macrocytic anemia can be caused by a nutritional deficiency of folate or vitamin B12 (typically causing a megaloblastic anemia) or by certain drugs or toxins (typically causing a nonmegaloblastic anemia.) Megaloblastic anemia is caused by ineffective erythropoiesis; megaloblasts can be identified on bone marrow aspirate.

The first step in identifying the correct cause of a macrocytic anemia should be a search for drugs and toxins. Hydroxyurea, zidovudine, chemotherapy, and alcohol are the most common offenders.<sup>33,34</sup>

If this search does not yield a likely source, the second step is to check B12 and folate levels. The serum levels of both cofactors can be obtained, although both have low sensitivity and specificity.<sup>34</sup> A low folate level suggests folate deficiency. The serum folate levels can change rapidly with dietary restriction and may be falsely elevated in B12 deficiency. RBC folate levels and homocysteine levels can be checked for confirmation of true folate deficiency; the homocysteine level is increased in folate deficiency.

Vitamin B12 deficiency is either caused by poor dietary intake or, more commonly, poor absorption. A false-low B12 level can be seen in pregnancy, oral contraceptive use, multiple myeloma, and in patients with leukopenia.<sup>33,34</sup> Normal to slightly high B12 levels do not completely exclude the diagnosis; therefore, methylmalonic acid and homocysteine levels can be performed to support the diagnosis. If B12 anemia is diagnosed, only a small percentage of this is actually caused by pernicious anemia, with a lack of gastric intrinsic factor.<sup>9</sup>

If a macrocytic anemia is not caused by nutritional deficiency or drugs or toxins, and the macrocytosis is marked, then primary bone marrow disease should be suspected. Mild or moderate macrocytosis should trigger reevaluation of the peripheral smear

looking for hemolysis (polychromasia), liver disease (target cells), or serum testing for hypothyroidism.<sup>33</sup>

## **Management Plan**

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### **Overview**

The initial treatment of anemia depends on the clinical status of patients. The cause will also guide further management. The most important decision for the EP is to initiate blood transfusion. The decision to initiate blood transfusion is not always straightforward, and it is not a decision that should be taken lightly. Transfusions carry the risk of infectious disease transmission as well as a wide range of potential transfusion reactions.<sup>35</sup> Also, blood products are relatively limited, with up to 3% of products crossmatched then subsequently wasted.<sup>36</sup>

**Unstable patients** In hemodynamically unstable patients with anemia or signs and symptoms of acute blood loss, the EP should always search for a source of active bleeding. As mentioned previously, in nontraumatic patients, the most common sources are GI, genitourinary and pulmonary sites. This source may be obvious on history or on physical examination. However, in the case of internal hemorrhage, other modalities of investigation (ultrasound, computed tomography, or endoscopy) may be necessary to identify the source. If a source is identified, efforts should be made to control the hemorrhage. These efforts may include involving surgery, GI, or other consultants, such as interventional radiology.

Patients who show signs of hemodynamic instability, ongoing hemorrhage, or tissue hypoxia need urgent blood transfusion. There is no clear hemoglobin level (ie, transfusion trigger) that should be used in unstable patients, as the measured laboratory value for hemoglobin lags behind clinical status in active bleeding. Crystalloid fluids may be used initially in fluid resuscitation to increase cardiac preload. However, because of the lack of oxygen-carrying capacity, crystalloid will only be a temporizing measure and blood transfusion should not be delayed. Uncrossmatched blood should be used in a life-threatening situation until fully crossmatched blood is available.<sup>29</sup> The rate of incompatible transfusion with uncrossmatched blood is 0.3% to 4.0%; therefore, attempts should be made, when time and clinical condition permits, to obtain fully crossmatched blood.<sup>37–39</sup> In patients requiring multiple units of packed RBCs for stabilization with uncontrolled hemorrhage, massive transfusion may be needed. Further information regarding massive transfusion protocols is available in the literature.

**Stable patients** In stable patients identified as having anemia, the EP must determine if further testing or intervention is indicated acutely. Not all patients require immediate investigation or treatment.

**Transfusion trigger** Clarifying the appropriate threshold to transfuse patients with anemia remains difficult, despite decades of research into the topic. A firm transfusion trigger, or hemoglobin level at which all patients should be transfused, remains elusive; the EP must carefully evaluate the entire clinical situation before initiating transfusion.

Historically, the 10/30 rule came about in 1942, when Adams and Lundy<sup>40</sup> suggested that patients be transfused if the hemoglobin was less than 10 g/dL.<sup>41</sup> This rule continued to be applied in the perioperative population in the 1980s and was extrapolated to all patients with anemia.<sup>40,42</sup> This rule was later refined to include only patients with cardiovascular disease because of studies suggesting patients had higher cardiovascular events if left with a hematocrit level of less than 28% to

30%.<sup>28,43</sup> However, further studies have not conclusively supported this 10/30 limit; this liberal transfusion trigger is no longer recommended.

Lower hemoglobin limits for transfusion are now used, and the limits are situationally defined and contextually applied. Evidence points to the success of using lower limits, but more research is needed. In the general population, using lower hemoglobin thresholds has been shown to diminish in-hospital mortality, but not adverse events or 30-day mortality.<sup>44–46</sup> In the acute upper GI hemorrhage population, such restrictive transfusion practices have demonstrated improved outcomes, including survival at 6 weeks after transfusion, decreased adverse events, and less rebleeding.<sup>47</sup>

What are those lower limits? In critically ill patients, research suggests using a transfusion trigger around 8.0 to 8.5 g/dL.<sup>42</sup> In non-critically ill anemic patients without cardiovascular disease, blood transfusion can be generally safely withheld until the hemoglobin reaches less than 7 g/dL.<sup>48</sup> In elderly patients, or those with ischemic heart disease, higher transfusion thresholds should be considered as there is concern that these populations may not be able to tolerate lower hemoglobin levels.<sup>41</sup>

Although these limits are widely used in clinical practice as transfusion triggers, the 2009 guidelines from the Society of Critical Care Medicine (SCCM), which are based on a substantial review of current literature and the risks associated with transfusion, virtually eliminate any hard transfusion trigger. The SCCM's guidelines place much more emphasis on the entire clinical picture: in hemodynamically stable patients, rather than establishing a strict transfusion guideline for hemoglobin levels of less than 7 g/dL, the patients' intravascular volume status, duration and extent of anemia, and cardiopulmonary physiologic factors should be taken into account.<sup>49</sup> In addition, when the decision to transfuse is made in stable patients with anemia but without active hemorrhage, the SCCM's guidelines suggest that only a single-unit transfusion should be performed except in the case of critical anemia. Posttransfusion hemoglobin values should be checked before initiating the transfusion of subsequent units.<sup>49</sup>

The debate regarding appropriate transfusion practices continues, and the individual EP is wise to consider the entire clinical context.

**Medications** Nutritional iron deficiency anemia can be treated with oral iron, which is fairly well tolerated and cost-effective.<sup>50</sup> The most common oral iron preparation therapy is ferrous sulfate given as 300 to 325 mg (equivalent to 60–65 mg elemental iron) 3 to 4 times daily without food to facilitate absorption.<sup>51</sup>

For the EP, it is reasonable to start empiric iron therapy without further work-up for iron deficiency anemia in women aged 18 to 39 years, in conjunction with clearly defined follow-up with a primary care doctor. However, in all other age groups and in all males, the EP should not start oral iron but rather refer patients to a primary care doctor, as pathologic conditions should be first ruled out before initiating iron supplementation therapy.<sup>11</sup>

In other forms of anemia, erythropoietic growth factors and B12 therapy may be given; but these treatments carry risks and significant costs and should generally be deferred to primary care or subspecialty consultants.<sup>11,52</sup>

**Consultations** Adults found to have iron deficiency anemia that is unexplained by routine laboratory investigations or obvious clinical presentation should have endoscopy performed as an outpatient. There is some evidence suggesting that patients older than 50 years have a colonoscopy performed first; if this does not reveal a source of bleeding, an esophagogastroduodenoscopy should then be performed. In patients less than 50 years of age, it has been suggested the reverse order of endoscopy be performed, but this has limited evidence.<sup>50</sup> Either way, if one endoscopy is negative, the other should be pursued.<sup>53</sup>

**Morbidity and mortality** There is limited research in regard to morbidity, mortality, and the quality-of-life effects of anemia.<sup>11</sup> Anemia does seem to have an impact on quality of life and can be a risk factor for all-cause mortality in the elderly, but quantifying that impact is difficult.<sup>11,14,54–56</sup> Anemia can contribute to an increased risk of falls as well as general functional impairment.<sup>57</sup> An observational study of Jehovah's Witness subjects with anemia demonstrated that low hemoglobin levels preoperatively increases mortality.<sup>58</sup> When coexisting with other diseases, such as chronic kidney disease, malignancy, and heart failure, anemia is found to be a risk factor for increased mortality.<sup>59</sup> Long-term severe anemia can lead to congestive heart failure, cardiovascular disease, and left ventricular hypertrophy.<sup>57</sup> Anemia is also linked to longer hospitalizations in the elderly.<sup>60</sup>

For the EP, anemia in the context of other comorbidities and acute disease processes can contribute to increased morbidity and mortality. However, except in a profound, acute hemorrhage, anemia is rarely a direct cause of death.<sup>58</sup>

### ***Special Populations: Anemia in Children***

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Anemia affects approximately 20% of American children at some point.<sup>1</sup> Normal values of CBC parameters are age adjusted, as are risk factors for the development of anemia. There is a normal physiologic nadir in hemoglobin levels around 6 to 8 weeks of life that reaches approximately 9 g/dL.<sup>1</sup>

The US Centers for Disease Control and Prevention and American Academy of Pediatrics<sup>61</sup> no longer recommend routine screening for anemia and instead limit their screening to those children at risk for anemia. The US Preventive Services Task Force (USPSTF) does not provide recommendations for or against screening.<sup>62</sup> It is still common practice for children to have a routine CBC done in infancy. As in adults, anemia is often discovered as an incidental finding.<sup>63</sup> One recent study documented an occult anemia rate of 13.9% (95% confidence interval 12.5%–15.4%) within a pediatric ED (aged 1–23 years). A discharge diagnosis of anemia was documented in only 8% of these patients. This finding represents a potential missed opportunity for intervention, although the implications remain unclear.<sup>64</sup>

The finding of anemia is never normal in a child and deserves further investigation. Anemia in childhood is diagnosed using the same parameters as in adults and should be investigated in the same fashion based on RBC indices to determine its possible cause. As in adults, anemia is typically caused by either decreased production or increased destruction. Iron deficiency anemia is common and can be treated, as in adults, with oral iron supplementation. There are a multitude of other causes, including inherited disorders, such as sickle cell disease or thalassemia.<sup>65</sup> Children who are found to have anemia during an ED visit should be referred back to the pediatrician or primary care provider.

### ***Disposition***

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Admission should be considered for patients with vital sign abnormalities that fail to readily improve, patients who have qualified for blood product transfusion, and patients with significant ongoing hemorrhage. As with other conditions, patients with comorbidities, such as advanced age, congestive heart failure, or severe renal disease, require a lower threshold for admission.

Patients who are hemodynamically stable without active hemorrhage and who show no signs of ischemia, acidosis, or impaired tissue perfusion can often be evaluated further in the outpatient setting.

Proper discharge planning from the ED is essential, with close follow-up with an appropriate consultant (eg, GI or gynecology, depending on the site of bleeding) or

with the primary care physician. Adequate discharge instructions include clear precautions for returning with worsening symptoms as well as a clear and specific follow-up plan.

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