# Chapter 122: Anemias

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## CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 33, Anemias.

## KEY CONCEPTS

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1. Anemia is a group of diseases characterized by a decrease in either hemoglobin (Hb) or the volume of red blood cells (RBCs), which results in decreased oxygen-carrying capacity of the blood. Anemia is defined by the World Health Organization (WHO) as Hb less than 13 g/dL (130 g/L; 8.07 mmol/L) in men and less than 12 g/dL (120 g/L; 7.45 mmol/L) in women.

2. Acute onset anemias are most likely to present with tachycardia, lightheadedness, and dyspnea. Chronic anemia often presents with weakness, fatigue, headache, vertigo, and pallor.

3. Iron-deficiency anemia (IDA) is characterized by decreased ferritin levels (most sensitive marker) and serum iron, and decreased transferrin saturation. Hb and hematocrit decrease later. RBC morphology includes hypochromia and microcytosis. Most patients are adequately treated with oral iron therapy, although parenteral iron therapy is necessary in some patients.

4. Vitamin $B_{12}$ deficiency, a macrocytic anemia, can be due to inadequate intake, malabsorption syndromes, and inadequate utilization. Anemia caused by lack of intrinsic factor, resulting in decreased vitamin $B_{12}$ absorption, is called *pernicious anemia.* Neurologic symptoms can be present and can become irreversible if the vitamin $B_{12}$ deficiency is not treated promptly. Oral or parenteral therapy can be used for replacement.

5. Folic acid deficiency, a macrocytic anemia, results from inadequate intake, decreased absorption, and increased folate requirements. Treatment consists of oral administration of folic acid, even for patients with absorption problems. Adequate folic acid intake is essential in women of childbearing age to decrease the risk of neural tube defects in their children.

6. Anemia of inflammation (AI) is a newer term used to describe both anemia of chronic disease and anemia of critical illness. AI is a diagnosis of exclusion. It results from chronic inflammation, infection, or malignancy and can occur as early as 1 to 2 months after the onset of the disease. The serum iron level is usually decreased, but in contrast to IDA, the serum ferritin concentration is normal or increased. Treatment is aimed at correcting the underlying pathology. Anemia of critical illness occurs within days of acute illness.

7. Anemia is a common problem in older adults, although not an inevitable complication of aging. Low Hb concentrations are not "normal" in older adults. Anemia is associated with an increased risk of hospitalization and mortality, reduced quality of life, and decreased physical functioning in older adults.

8. IDA is a leading cause of infant morbidity and mortality worldwide. Age- and sex-adjusted norms must be used to interpret laboratory results for pediatric patients. Primary prevention of IDA is the goal because physical and mental developmental delays can be irreversible.

## PATIENT CARE PROCESS

### Patient Care Process for Anemia


### Collect

- Patient characteristics (eg, age, race, sex, pregnancy)
- Patient history (eg, past medical history, dietary habits, physical activity, alcohol intake, smoking status, chemical exposure)
- Symptoms of anemia (eg, fatigue, weakness, chest pain, dizziness, pallor, see "Clinical Presentation: Anemia" box)
- Current medications (including over-the-counter and supplements)
- Objective data (see "Clinical Presentation: Anemia" box)
  - Blood pressure (BP), heart rate (HR)
  - Labs (CBC, iron studies, vitamin $B_{12}$, folate, homocysteine, MMA, etc.)

### Assess

- Underlying disease states (blood loss, heart failure, chronic renal disease, HIV, malignancy; see Table 122-1)
- Dietary habits and potential social factors contributing to nutritional deficiencies
- Acuity of symptoms and need for transfusion or hospitalization
- Current medications that may contribute to or worsen anemia or blood loss
- Lab results to determine underlying etiology of anemia for proper treatment selection or attainment of treatment goals
- Ability to self-inject medications (eg, cyanocobalamin)

### Plan*

- Dietary interventions for nutritional deficiencies
- Initiate appropriate drug therapy treatment based on etiology (correct formulation, strength, dosing, frequency, and address pertinent drug interactions [see Table 122-3 for iron product selection/drug interactions])

- Monitoring for efficacy and safety (labs and symptom improvement, corrected etiology if possible, adverse drug reactions)
- Patient education (expectations/purpose of treatment, adverse effects, diet modifications, etc.)
- Improved treatment of underlying pathologies if contributing to anemia of chronic disease

**Implement***

- Educate patient on treatment interventions and treatment expectations
- Reinforce adherence to treatment plan for short- and long-term success
- Schedule patient for follow-up at appropriate intervals

**Follow-up: Monitor and Evaluate**

- Lab values within 4 weeks after treatment initiation
- Tolerability of medications
- Symptom improvement (eg, fatigue, pallor, weakness, dizziness, neuropathy)
- If minimal improvement or worsening, determine whether etiology of anemia was correct

****Collaborate with patient, caregivers, and other healthcare professionals.***

## BEYOND THE BOOK

**BEYOND THE BOOK**

Watch the Khan Academy video on the pathophysiology of anemia:

https://tinyurl.com/5n8eb5dx

Write a paragraph that explains the pathophysiology of anemia to a patient. You can only use patient friendly language.

## INTRODUCTION

Anemia affects almost one-third of the world's population, with developing countries carrying the highest burden.[1] Anemia is defined by the WHO as hemoglobin (Hb) less than 13 g/dL (130 g/L; 8.07 mmol/L) in men or less than 12 g/dL (120 g/L; 7.45 mmol/L) in women.[2] In the United States, about 3 million people have anemia.[3] Millions of people are unaware they have anemia, making it one of the most underdiagnosed conditions in the United States. Iron deficiency is the leading cause of anemia worldwide, accounting for as many as 50% of cases.[2] Although nutritional deficiencies occur less often in the United States, they can occur in at risk populations (discussed in more detail later). Anemia is not an innocent bystander because it can affect both length and quality of life. Retrospective observational studies of hemodialysis patients and heart failure patients suggest that anemia is an independent risk factor for mortality.[4] In addition, anemia significantly influences morbidity in patients with end-stage renal disease, chronic kidney disease, and heart failure.[5] Anemia is associated with psychomotor and cognitive abnormalities in children. Similarly, anemia is associated with cognitive dysfunction in patients with renal failure or cancer, and among community-dwelling elders.[6] Anemia during pregnancy is associated with increased risk for low birth weights, preterm delivery, and perinatal mortality.[7] Maternal IDA may be associated with postpartum depression in mothers and poor performance by offspring on mental and psychomotor tests. In older adults, anemia is associated with a greater risk for falls and

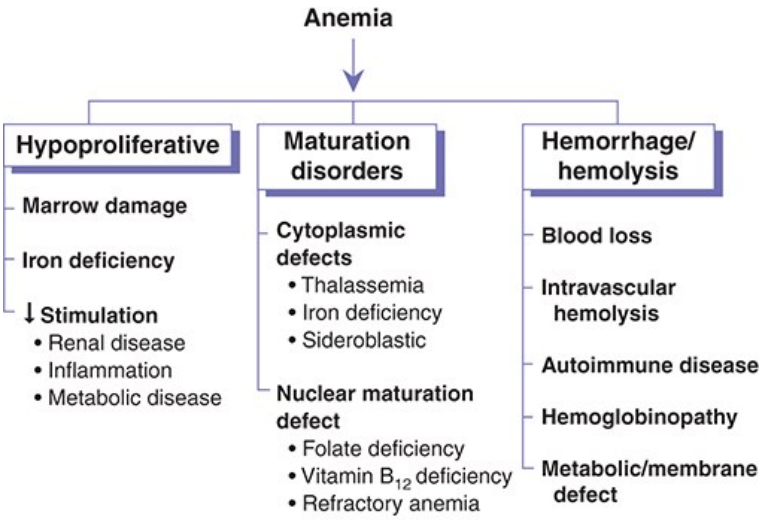
dementia.[8] Global goals of treatment in anemic patients are to alleviate signs and symptoms, correct the underlying etiology, and prevent recurrence of anemia.

Anemia is a group of diseases characterized by a decrease in Hb or circulating red blood cells (RBCs), resulting in reduced oxygen-carrying capacity of the blood. Anemia can result from inadequate RBC production, increased RBC destruction, or blood loss. It can be a manifestation of systemic disorders, such as infection, chronic renal disease, or malignancy. Anemia is often a sign of underlying pathology, and rapid diagnosis of the cause may be essential.

Figure 122-1 shows the functional classification of anemia. This chapter focuses on some of the most common causes of anemia—IDA, vitamin $B_{12}$ or folic acid deficiency, and anemia of inflammation (AI) (eg, anemia of chronic disease [ACD]). Some of the other common causes of anemia are discussed in other chapters (cancer, renal disease). Drugs can also cause hematologic disorders, including anemia.

**FIGURE 122-1**

Functional classification of anemia.




Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*


Characteristic changes in the RBC size based on erythrocyte indices can be the first step in the morphologic classification and understanding of the anemia. Anemia can be classified by RBC size such as macrocytic, normocytic, or microcytic. Both vitamin $B_{12}$ deficiency and folic acid deficiency are macrocytic anemias. An example of a microcytic anemia is iron deficiency, whereas a normocytic anemia may be associated with recent blood loss or chronic disease. More than one etiology of anemia can occur concurrently. Mixed anemias occur more commonly in older adults.

Microcytic anemias result from a quantitative deficiency in Hb synthesis, usually due to iron deficiency or impaired iron utilization. As a result, erythrocytes containing insufficient Hb are formed. Microcytosis and hypochromia are the morphologic abnormalities that provide evidence of impaired Hb synthesis.

Macrocytic anemias can be divided into megaloblastic and nonmegaloblastic anemias. The type of macrocytic anemia can be distinguished microscopically by peripheral blood smear examination. Megaloblasts are distinctive cells that express a biochemical abnormality of impaired DNA synthesis, resulting in unbalanced cell growth. Megaloblastic anemias may affect all hematopoietic cell lines. The most common causes of megaloblastic anemia discussed in this chapter are vitamin $B_{12}$ and folate deficiency. Nonmegaloblastic macrocytic anemias may arise from liver disease, hypothyroidism, hemolytic processes, and alcoholism.

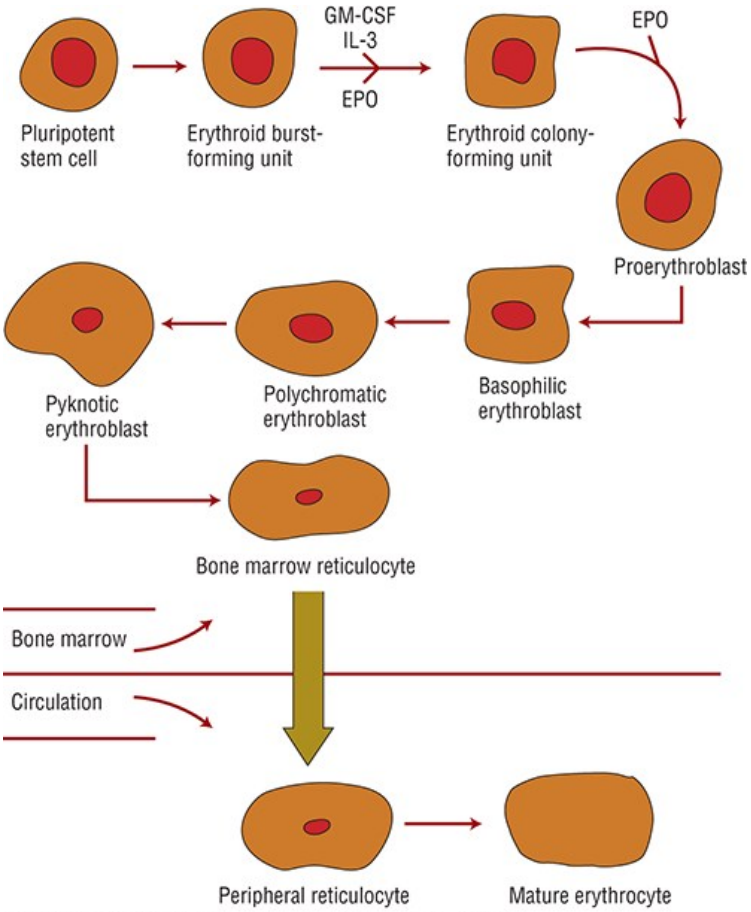
## MATURATION AND DEVELOPMENT OF RED BLOOD CELLS

In adults, RBCs are formed in the marrow of the vertebrae, ribs, sternum, clavicle, pelvic (iliac) crest, and proximal epiphyses of the long bones. In children, most bone marrow space is hematopoietically active to meet increased RBC requirements.

In normal RBC formation, a pluripotent stem cell yields an erythroid burst-forming unit. Erythropoietin (EPO) and cytokines such as interleukin-3 and granulocyte-macrophage colony-stimulating factor stimulate this cell to form an erythroid colony-forming unit in the marrow (Fig. 122-2). During this process, the nucleus becomes smaller with each division, finally disappearing in the normal erythrocyte. Hb and iron are incorporated into the gradually maturing RBC, which eventually is released from the marrow into the circulating blood as a reticulocyte. The maturation process usually takes about 1 week. The reticulocyte loses its nucleus and becomes an erythrocyte within several days. The circulating erythrocyte is a non-nucleated, nondividing cell. More than 90% of the protein content of the erythrocyte consists of the oxygen-carrying molecule Hb. Erythrocytes have a normal survival time of about 120 days.[9]

**FIGURE 122-2**

Erythrocyte maturation sequence.




Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

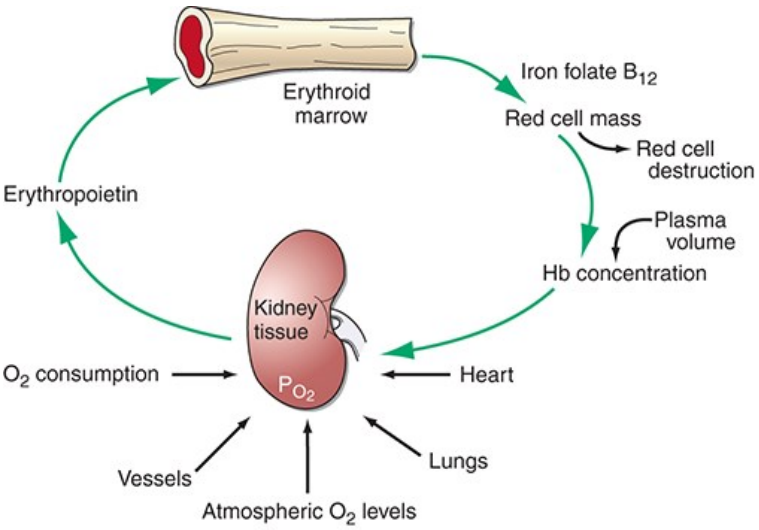

## Stimulation of Erythropoiesis

The hormone EPO, 90% of which is produced by the kidneys, initiates and stimulates RBC production. Erythropoiesis is regulated by a feedback loop (Fig. 122-3). The primary mechanism of action of EPO is to prevent apoptosis, or programmed cell death, of erythroid precursor cells and allow their proliferation and subsequent maturation. A decrease in tissue oxygen concentration signals the kidneys to increase the production and release of EPO into the plasma, which increases production and maturation of RBCs. Under normal circumstances, the RBC mass is kept at an almost constant level by EPO matching new erythrocyte production to the natural rate of loss of RBCs. Early appearance of large quantities of reticulocytes in the peripheral

circulation (reticulocytosis) is an indication of increased RBC production.[9]

FIGURE 122-3

Physiologic regulation of red cell production by tissue oxygen tension. *(Reproduced, with permission, from Adamson JW, Longo DL. Anemia and polycythemia. In: Longo DL, Fauci AS, Kasper DL, et al., eds. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw Hill; 2012.)*






## Incorporation of Iron into Heme

Iron is an essential part of Hb. The specific plasma transport protein transferrin delivers iron to the bone marrow for incorporation into the Hb molecule. Transferrin enters cells by binding to transferrin receptors, which circulate and then attach to cells needing iron. Fewer transferrin receptors are present on the surface of cells that do not need iron, thus preventing iron-replete cells from receiving excess iron.[10]

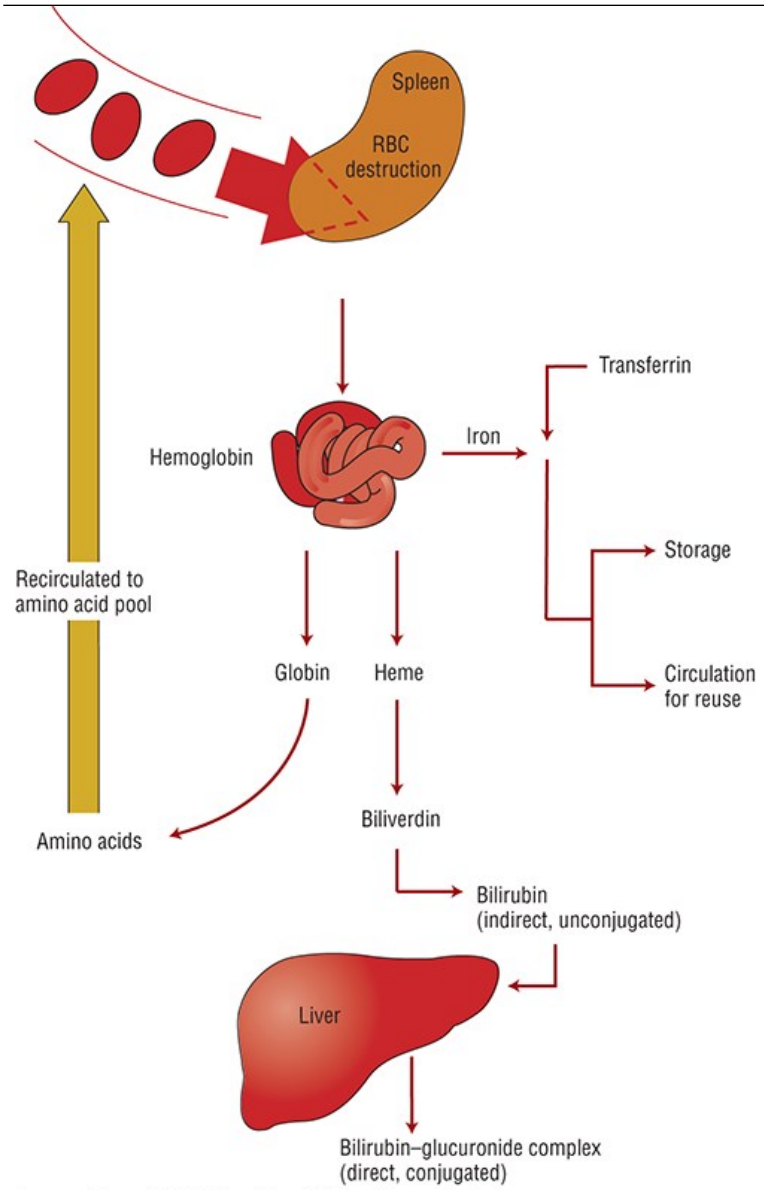
Circulating transferrin normally is about 30% saturated with iron. Transferrin delivers extra iron to other body storage sites, such as the liver, marrow, and spleen, for later use. This iron is stored within macrophages as ferritin or hemosiderin. Ferritin consists of a $Fe^{3+}$ hydroxyphosphate core surrounded by a protein shell called *apoferritin*. Hemosiderin can be described as compacted ferritin molecules with an even greater iron-to-protein shell ratio. Physiologically it is a more stable, but less available, form of storage iron. Since total body iron storage is generally reflected by ferritin levels, low serum ferritin levels provide strong evidence of IDA.[9]

## Normal Destruction of Red Blood Cells

Phagocytic breakdown destroys older blood cells, primarily in the spleen but also in the marrow (Fig. 122-4). The Hb in RBCs destroyed by intravascular hemolysis becomes attached to haptoglobin and is carried back to the marrow for processing in the normal manner.[11]

FIGURE 122-4

Destruction of red blood cells.

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## DIAGNOSIS OF ANEMIA

### General Presentation

History, physical examination, and laboratory testing are used to evaluate the patient with anemia. The workup determines if the patient is bleeding and investigates potential causes of the anemia, such as increased RBC destruction, bone marrow suppression, and iron deficiency. Diet can be important in identifying the causes of anemia. Additionally, information about concurrent nonhematologic disease states and a drug history are essential when evaluating the cause of the anemia (Chapter e125, "Drug-Induced Hematologic Disorders"). History of blood transfusions and exposure to toxic chemicals also should be obtained.

Presenting signs and symptoms of anemia depend on its rate of development and the patient's age and cardiovascular status. The severity of symptoms does not always correlate with the degree of anemia. Healthy patients may acclimate to low Hb concentrations if the anemia develops slowly. Mild anemia often is associated with no clinical symptoms and may be found incidentally upon obtaining a complete blood count (CBC) for

other reasons. The signs and symptoms in older adults with anemia may be incorrectly attributed to their age or concomitant disease states. Older adults may not tolerate lower levels of Hb in the same way that younger persons do. Similarly, patients with cardiac or pulmonary disease may be less tolerant of mild anemia. Premature infants with anemia may be asymptomatic or have tachycardia, poor weight gain, increased supplemental oxygen needs, or episodes of apnea or bradycardia.

2 Anemia of rapid onset is most likely to present with cardiopulmonary symptoms such as palpitations, angina, lightheadedness, and shortness of breath due to decreased oxygen delivery to tissues or hypovolemia in those with acute bleeding. The patient also may have tachycardia and hypotension.

If onset is more chronic, presenting symptoms may include fatigue, weakness, headache, orthopnea, dyspnea on exertion, vertigo, faintness, sensitivity to cold, and pallor. These traditional signs of anemia have limited sensitivity and specificity and may be misinterpreted. With chronic bleeding, equilibration within the extravascular space occurs, so cardiopulmonary symptoms are less common.

Possible manifestations of IDA include glossal pain, smooth tongue, reduced salivary flow, pica (compulsive eating of nonfood items), and pagophagia (compulsive eating of ice). These symptoms are not likely to appear unless the anemia is severe.

Neurologic findings in vitamin $B_{12}$ deficiency may precede hematologic changes. Early neurologic findings may include numbness and paraesthesias, which are typically bilateral and affect lower limbs more frequently. Ataxia, spasticity, diminished vibratory sense, decreased proprioception, and imbalance may occur later as demyelination of the dorsal columns and corticospinal tract develop. Vision changes may result from optic nerve involvement. Psychiatric findings include irritability, personality changes, memory impairment, depression, and infrequently, psychosis.

**CLINICAL PRESENTATION: Anemia**

### General

- Patients may be asymptomatic or have vague complaints
- Patients with vitamin $B_{12}$ deficiency may develop neurologic complications
- In AI, signs and symptoms of the underlying disorder often overshadow those of the anemia

### Symptoms

- Decreased exercise tolerance
- Fatigue
- Dizziness
- Irritability
- Weakness
- Palpitations
- Vertigo
- Shortness of breath
- Chest pain
- Neurologic symptoms in vitamin $B_{12}$ deficiency

### Signs

- Tachycardia
- Pale appearance (most prominent in conjunctivae)
- Decreased mental acuity
- Increased intensity of some cardiac valvular murmurs
- Diminished vibratory sense or gait abnormality in vitamin $B_{12}$ deficiency

### Laboratory Tests

- Hemoglobin, hematocrit, and RBC indices may remain normal early in the disease and then decrease as the anemia progresses
- Serum iron is low in IDA and AI
- Ferritin levels are low in IDA and normal or elevated in AI
- Total iron-binding capacity is high in IDA and is low or normal in AI
- Mean cell volume is elevated in vitamin $B_{12}$ deficiency and folate deficiency
- Vitamin $B_{12}$ and folate levels are low in their respective types of anemia
- Homocysteine is elevated in vitamin $B_{12}$ deficiency and folate deficiency
- Methylmalonic acid is elevated in vitamin $B_{12}$ deficiency

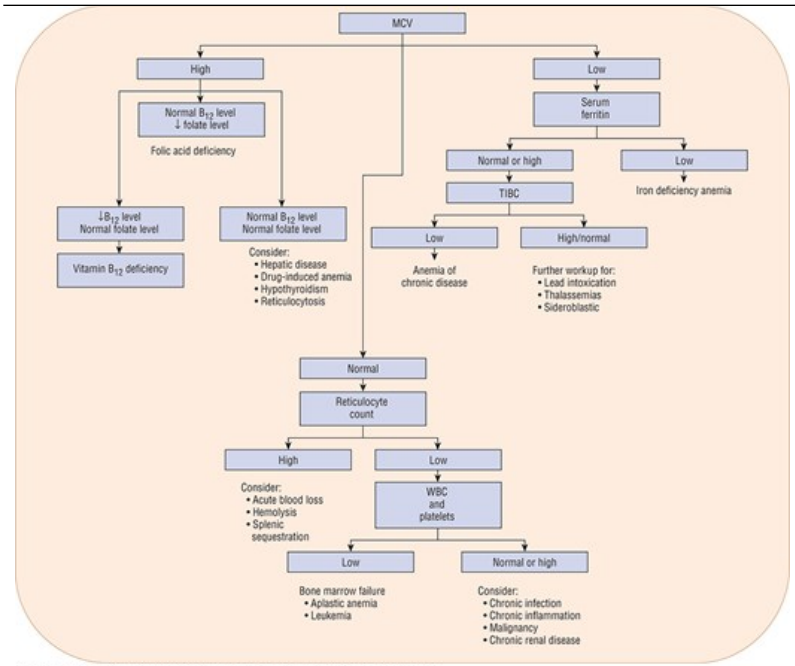
## Laboratory Evaluation

The initial evaluation of anemia involves a CBC (including RBC indices), reticulocyte index, and possibly an examination of a stool sample for occult blood if bleeding is suspected. The results of the initial evaluation determine the need for other studies, such as examination of a peripheral blood smear. Based on laboratory test results, anemia can be categorized into three functional defects: RBC production failure (hypoproliferative), cell maturation ineffectiveness, or increased RBC destruction or loss (see Fig. 122-1).

Figure 122-5 shows a broad, general algorithm for the diagnosis of anemia based on laboratory data. There are many exceptions and additions to this algorithm, but it can serve as a guide to the typical presentation of common types and causes of anemia. The algorithm is less useful in the presence of more than one cause of anemia.

**FIGURE 122-5**

General algorithm for diagnosis of anemias based on laboratory data.






### Hemoglobin

Values given for Hb represent the amount of Hb per volume of whole blood. The higher values seen in males are due to stimulation of RBC production by androgenic steroids, while the lower values in females reflect the decrease in Hb as a result of blood loss during menstruation. The Hb level can be used as a rough estimate of the oxygen-carrying capacity of blood. Hb levels may be diminished because of a decreased quantity of Hb per RBC or a decrease in the actual number of RBCs.

### Hematocrit

Expressed as a percentage, hematocrit (Hct) is the actual volume of RBCs in a unit volume of whole blood. It is generally about three times the Hb value (when Hb is expressed in g/dL). An alteration in this ratio may occur with abnormal cell size or shape and often indicates pathology. A low Hct indicates a reduction in either the number or the size of RBCs or an increase in plasma volume.

### Red Blood Cell Count

The RBC count is an indirect estimate of the Hb content of the blood; it is an actual count of RBCs per unit of blood.

### Red Blood Cell Indices

Wintrobe indices describe the size and Hb content of the RBCs and are calculated from the Hb, Hct, and RBC count. RBC indices, such as mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), are single mean values that do not express the variation that can occur in cells.

#### Mean Corpuscular Volume

MCV represents the average volume of RBCs. It may reflect changes in MCH. Cells are considered macrocytic if they are larger than normal, microcytic if they are smaller than normal, and normocytic if their size falls within normal limits. Folic acid– and vitamin $B_{12}$–deficiency anemias yield macrocytic cells, whereas iron deficiency is an example of a microcytic anemia. When IDA (decreased MCV) is accompanied by folate deficiency (increased MCV), the overall MCV may be normal. Failure to understand that the MCV represents an average RBC size can cause the clinician to potentially overlook some causes of the anemia.

#### Mean Corpuscular Hemoglobin

MCH is the amount of Hb in a RBC, and usually increases or decreases with the MCV. Two morphologic changes, microcytosis and hypochromia, can reduce MCH. A microcytic cell contains less Hb because it is a smaller cell, while a hypochromic cell has a low MCH because of the decreased concentration of Hb present in the cell. Cells can be both microcytic and hypochromic, as seen with IDA. The MCH alone cannot distinguish between microcytosis and hypochromia. The most common cause of an elevated MCH is macrocytosis (eg, vitamin $B_{12}$ or folate deficiency).

#### Mean Corpuscular Hemoglobin Concentration

The concentration of Hb per volume of cells is the mean cell Hb concentration (MCHC). Because MCHC is independent of cell size, it is more useful than MCH in distinguishing between microcytosis and hypochromia. A low MCHC indicates hypochromia; a microcyte with a normal Hb concentration will have a low MCH but a normal MCHC. A decreased MCHC is seen most often in IDA.

### Total Reticulocyte Count

The total reticulocyte count is an indirect assessment of new RBC production. It reflects how quickly immature RBCs (reticulocytes) are produced by bone marrow and released into the blood. Reticulocytes circulate in the blood about 2 days before maturing into RBCs. About 1% of RBCs are normally replaced daily, representing a reticulocyte count of 1%. The reticulocyte count in normocytic anemia can differentiate hypoproliferative marrow from a compensatory marrow response to anemia (see Fig. 122-5). A lack of reticulocytosis in anemia indicates impaired RBC production. Examples include iron deficiency, $B_{12}$ deficiency, ACD, malnutrition, renal insufficiency, and malignancy. A high reticulocyte count may be seen in acute blood loss or hemolysis.

### Red Blood Cell Distribution Width

The higher the red blood cell distribution width (RDW), the more variable is the size of the RBCs. The RDW increases in early IDA because of the release of large, immature, nucleated RBCs to compensate for the anemia, but this change is not specific for IDA. The RDW can also be helpful in the diagnosis of a mixed anemia. A patient can have a normal MCV yet have a wide RDW. This finding indicates the presence of microcytes and macrocytes, which would yield a “normal” average RBC size. The use of RDW to distinguish IDA from ACD is not recommended.

### Peripheral Blood Smear

The peripheral blood smear can supplement other clinical data and help establish a diagnosis. Peripheral blood smears provide information on the functional status of the bone marrow and defects in RBC production. Additionally, it provides information on variations in cell size (anisocytosis) and shape (poikilocytosis). Blood smears are placed on a microscope slide and stained as appropriate. Morphologic examination includes assessment of size, shape, and color. The extent of anisocytosis correlates with increased range of cell sizes. Poikilocytosis can suggest a defect in the maturation of RBC precursors in the bone marrow or the presence of hemolysis.

### Serum Iron

The level of serum iron is the concentration of iron bound to transferrin. Transferrin is normally about one-third bound (saturated) to iron. The serum iron level of many patients with IDA may remain within the lower limits of normal because a considerable amount of time is required to deplete iron stores. Serum iron levels show diurnal variation (higher in the morning, lower in the afternoon), but this variation is probably not clinically significant.[12] Since serum iron levels are decreased by infection and inflammation, serum iron levels are best interpreted in conjunction with the total iron-binding capacity (TIBC). The serum iron level decreases with IDA and ACD and increases with hemolytic anemias and iron overload.

### Total Iron-Binding Capacity

TIBC is an indirect measurement of the iron-binding capacity of serum transferrin. Normally, about 30% of available iron binding sites are filled. With this laboratory test, all binding sites are filled to measure TIBC; the excess (unbound) iron is then removed and the serum iron concentration determined. Unlike the serum iron level, the TIBC does not fluctuate over hours or days. TIBC usually is higher than normal when body iron stores are low. The finding of a low serum iron level and a high TIBC suggests IDA. The TIBC is actually a measurement of protein serum transferrin, which can be affected by a variety of factors. Patients with infection, malignancy, inflammation, liver disease, and uremia may have a decreased TIBC and a

decreased serum iron level, which are consistent with the diagnosis of ACD.

### Percentage Transferrin Saturation

The ratio of serum iron level to TIBC indicates transferrin saturation. It reflects the extent to which iron-binding sites are occupied on transferrin and indicates the amount of iron readily available for erythropoiesis. It is expressed as a percentage, as described in the following formula:

$$\text{Transferrin saturation} = \frac{\text{serum iron}}{\text{TIBC}} \times 100$$Transferrin saturation=serum ironTIBC×100

Transferrin normally is 20% to 50% saturated with iron. In IDA, transferrin saturation of 15% or lower is commonly seen.[11] Transferrin saturation is a less sensitive and specific marker of iron deficiency than ferritin levels.

### Serum Ferritin

The serum concentration of ferritin (storage iron) is proportional to total iron stores and therefore is the best indicator of iron deficiency or iron overload. Ferritin levels indicate the amount of iron stored in the liver, spleen, and bone marrow cells. Low serum ferritin levels are virtually diagnostic of IDA. In contrast, serum iron levels may decrease in both IDA and ACD. Since serum ferritin is an acute phase reactant, chronic infection or inflammation can increase its concentration independent of iron status, masking depleted tissue stores. This limits the utility of the serum ferritin if the level is normal or high for a chronically ill patient. For these patients, iron, even if present in these tissue stores, may not be available for erythropoiesis.

### Folic Acid

The results of folic acid measurements vary depending on the assay method used. Decreased serum folic acid levels (less than 4 ng/mL [9 nmol/L]) indicate a folate deficiency anemia that may coexist with a vitamin $B_{12}$–deficiency anemia. Erythrocyte folic acid levels are less variable than serum levels because they are slow to decrease in an acute process such as drug-induced folic acid deficiency and slow to increase with oral folic acid replacement. In addition, erythrocyte folic acid levels have the theoretical advantage of less susceptibility to rapid changes in diet and alcohol intake. Limitations with sensitivity and specificity do exist with measurements of erythrocyte folate. If the serum folate concentration is normal for a patient with suspected folate deficiency, then the erythrocyte folate level should be measured.[13]

### Vitamin $B_{12}$

Low levels (less than 200 pg/mL [148 pmol/L]) of vitamin $B_{12}$ (cyanocobalamin or cobalamin) indicate deficiency. However, a deficiency may exist prior to the recognition of low serum levels. Serum values are maintained at the expense of vitamin $B_{12}$ tissue stores. Vitamin $B_{12}$ and folate deficiency may overlap, thus serum levels of both vitamins should be determined. Vitamin $B_{12}$ levels may be falsely low with folate deficiency and pregnancy.[11]

### Schilling Test

This test used to be the “gold standard” for assessing vitamin $B_{12}$ absorption. Due to its cost, unavailable test components, and complexity, the test is no longer available.[14]

### Homocysteine

Vitamin $B_{12}$ and folate are required for the conversion of homocysteine to methionine. Increased serum homocysteine may suggest vitamin $B_{12}$ or folate deficiency. Homocysteine levels can also be elevated in patients with vitamin $B_6$ deficiency, renal failure, and hypothyroidism.[15]

### Methylmalonic Acid

A vitamin $B_{12}$ coenzyme is needed to convert methylmalonyl coenzyme A to succinyl coenzyme A. Patients with vitamin $B_{12}$ deficiency have increased concentrations of serum methylmalonic acid (MMA), which is a more specific marker for vitamin $B_{12}$ deficiency than homocysteine. MMA levels are not

elevated in folate deficiency because folate does not participate in MMA metabolism. Levels of both MMA and homocysteine usually are elevated prior to the development of hematologic abnormalities and reductions in serum vitamin $B_{12}$ levels.[11]

## IRON-DEFICIENCY ANEMIA

### Epidemiology

Iron deficiency is the most common nutritional deficiency in developing and developed countries. Data from the National Health and Nutrition Examination Survey (NHANES) indicate the prevalence of iron deficiency in the United States in toddlers (1-2 years) and women of childbearing age is 7% and 12%, respectively.[16] Iron deficiency may precede the appearance of anemia because of the wide normal ranges for Hb and Hct.

### Iron Balance

The normal iron content of the body is about 3 to 4 g. Iron is a component of Hb, myoglobin, and cytochromes. About 2 g of the iron exists in the form of Hb, and about 130 mg exists as iron-containing proteins such as myoglobin. About 3 mg of iron is bound to transferrin in plasma, and 1,000 mg of iron exists as storage iron in the form of ferritin or hemosiderin. The rest of the iron is stored in other tissues such as cytochromes.[12] Due to the toxicity of inorganic iron, the body has an intricate system for iron absorption, transport, storage, assimilation, and elimination. Hepcidin is a regulator of intestinal iron absorption, iron recycling, and iron mobilization from hepatic stores. It is a peptide hormone made in the liver, distributed in plasma, and excreted in urine. Hepcidin inhibits efflux of iron through ferroportin. Hepcidin synthesis is increased by iron loading and inflammation and decreased by iron deficiency and erythropoietic activity. Hepcidin is induced during infections and inflammation, which allows iron to sequester in macrophages, hepatocytes, and enterocytes.[158] As a result, hepcidin is likely an important mediator of AI. Hepcidin is usually suppressed in IDA.[17] Hepcidin testing is not routinely available.[18]

Most people lose about 1 mg of iron daily. Menstruating women can lose up to 0.6% to 2.5% more per day. Pregnancy requires additional iron and a blood donation can result in as much as 250 mg of iron loss;[19] these individuals are at higher risk for deficiency.

The daily recommended dietary allowance for iron is 8 mg in adult males and postmenopausal females and 18 mg in menstruating females. Children require more iron because of growth-related increases in blood volume, and pregnant women have an increased iron demand brought about by fetal development. In the absence of hemochromatosis, iron overload does not occur because only the amount of iron lost per day is absorbed. The amount of iron absorbed from food depends on body stores, the rate of RBC production, the type of iron provided in the diet, and the presence of any substances that may enhance or inhibit iron absorption.

Heme iron is found in meat, fish, and poultry, and is about three times more absorbable than the nonheme iron found in vegetables, fruits, dried beans, nuts, grain products, and dietary supplements. Gastric acid and other dietary components such as ascorbic acid increase the absorption of nonheme iron. Dietary components that form insoluble complexes with iron (phytates, tannates, and phosphates) decrease absorption. Phytates, a natural component of grains, brans, and some vegetables, can form poorly absorbed complexes and partially explain the increased prevalence of IDA in poorer countries, where grains and vegetables compose a disproportionate amount of the normal diet. Polyphenols bind iron and decrease nonheme iron absorption when large amounts of tea or coffee are consumed with a meal. Although the mechanism is unknown, calcium inhibits absorption of both heme and nonheme iron. Finally, because gastric acid improves iron absorption, patients who have had a gastrectomy or achlorhydria have decreased iron absorption.[20,21]

### Etiology

Iron deficiency results from prolonged negative iron balance, which can occur due to increased iron demand or hematopoiesis, increased loss, or decreased intake/absorption. The onset of iron deficiency depends on an individual's initial iron stores and the imbalance between iron absorption and loss. Multiple etiologic factors usually are involved. Certain groups at higher risk for iron deficiency include children younger than 2 years, adolescent girls, pregnant/lactating females, and those older than 65 years. Blood loss should initially be considered a cause of IDA in adults.[22] Blood loss may occur as a result of many disorders, including trauma, hemorrhoids, peptic ulcers, gastritis, GI malignancies, arteriovenous malformations, diverticular disease, copious menstrual flow, nosebleeds, and postpartum bleeding. In less industrialized nations, the risk of IDA is largely related to dietary factors.

Pregnant women should be screened for anemia at their first prenatal visit, but the United States Preventive Services Task Force (USPSTF) no longer recommends routine screening for IDA in all asymptomatic pregnant women.[23] If a pregnant patient is anemic on screening, they should be evaluated for all types of anemia, with iron deficiency being the most common. The Centers for Disease Control and Prevention (CDC) recommends initiation of low-dose iron supplements or prenatal vitamins with 30 mg/day of iron at each woman's first prenatal visit to compensate for the increased iron demands during pregnancy.[24]

Medication history, specifically regarding recent or past use of iron, alcohol, corticosteroids, anticoagulants, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs), is a vital part of the history to assess bleeding risk. Other possible causes of hypochromic microcytic anemia include AI, thalassemia, sideroblastic anemia, and heavy metal (mostly lead) poisoning (see Fig. 122-4).

## Pathophysiology

Iron is vital to the function of all cells. Manifestations of iron deficiency occur in three stages. In the initial stage, iron stores are reduced without reduced serum iron levels and can be assessed with serum ferritin measurement. The stores allow iron to be utilized when there is an increased need for Hb synthesis. Once stores are depleted, there still is adequate iron from daily RBC turnover for Hb synthesis. Further iron losses would make the patient vulnerable to anemia development. In the second stage, iron deficiency occurs when iron stores are depleted, and Hb is above the lower limit of normal for the population, but may be reduced for a given patient. Findings include reduced transferrin saturation and increased TIBC. The third stage occurs when the Hb falls to less than normal values.

## Laboratory Findings

3 Abnormal laboratory findings for patients with IDA generally include low serum iron and ferritin levels and high TIBC. In the early stages of IDA, RBC size is not changed. Low ferritin concentration is the earliest and most sensitive indicator of iron deficiency. However, ferritin may not correlate with iron stores in the bone marrow because renal or hepatic disease, malignancies, infection, or inflammatory processes may increase ferritin values.[12] Hb, Hct, and RBC indices usually remain normal in early stages. In the later stages of IDA, Hb, and Hct fall below normal values, and a microcytic hypochromic anemia develops. Even slightly abnormal Hb and Hct levels may indicate significant depletion of iron stores and should not be ignored. In terms of RBC indices, MCV is reduced earlier in IDA than Hb concentration.

Transferrin saturation (ie, serum iron level divided by the TIBC) is helpful for assessing IDA. Low values may indicate IDA, although low serum transferrin saturation values also may be present in inflammatory disorders. The TIBC may help to differentiate the diagnosis in these patients. Elevated TIBC levels suggest IDA, while low values represent inflammatory disease.

## Treatment

### Desired Outcomes

The outcomes for all types of anemia include reversal of hematologic parameters to normal, return of normal function and quality of life, and prevention or reversal of long-term complications, such as neurologic complications of vitamin $B_{12}$ deficiency.

### Dietary Supplementation and Oral Iron Preparations

The severity and cause of IDA determine the approach to treatment. Treatment is focused on replenishing iron stores. Because iron deficiency can be an early sign of other illnesses, treatment of the underlying disease may aid in the correction of iron deficiency.

Treatment of IDA usually consists of administration of oral or parenteral iron preparations. Examples of foods that are high in iron include animal liver, fortified cereals/oatmeal, beef, eggs, spinach, lentils, tofu, and beans. Iron is best absorbed from meat, fish, and poultry. These foods as well as certain iron-fortified cereals can help treat IDA if diet is a major factor in deficiency. Milk and tea reduce absorption of iron and should be consumed in moderation. In many cases of IDA, oral administration of iron therapy with soluble $Fe^{2+}$ iron salts is an appropriate first step.

$Fe^{2+}$ sulfate, succinate, lactate, fumarate, glutamate, and gluconate have similar oral absorption. Ferric citrate was approved by the Food and Drug

Administration (FDA) in 2017 to treat IDA in adults with chronic kidney disease who are not on dialysis (see Chapter 63). Iron is best absorbed in the reduced $Fe^{2+}$ form, with maximal absorption occurring in the duodenum, primarily due to the acidic medium of the stomach. Slow-release, sustained-release, or enteric coated iron preparations may not undergo sufficient dissolution until they reach the small intestine. In the alkaline environment of the small intestine, iron tends to form insoluble complexes, which significantly reduces absorption. The dose of iron replacement therapy depends on the patient's ability to tolerate the administered iron. Tolerance of iron salts improves with a small initial dose and gradual escalation to the full dose. For patients with IDA, the generally recommended dose is about 150 to 200 mg of elemental iron daily, usually in two or three divided doses to maximize tolerability. If patients cannot tolerate this daily dose of elemental iron, smaller amounts of elemental iron (eg, single 325-mg tablet of $Fe^{2+}$ sulfate) usually are sufficient to replace iron stores, although at a slower rate. Table 122-1 lists the percentage of elemental iron of commonly available iron salts. Iron preferably is administered at least 1 hour before meals because food can interfere with iron absorption. Many patients must take iron with food because they experience GI upset when iron is administered on an empty stomach.

TABLE 122-1

**Oral Iron Products**

| Iron Salt | Percent Elemental Iron | Common Formulations and Elemental Iron Provided |
|---|---|---|
| Ferrous sulfate | 20 | 60-65 mg/324-325 mg tablet<br>44 mg/5 mL elixir<br>15 mg/1 mL solution |
| Ferrous gluconate | 12 | 38 mg/325 mg tablet<br>28-29 mg/240-246 mg tablet |
| Ferrous fumarate | 33 | 66 mg/200 mg tablet<br>106 mg/324-325 mg tablet |
| Ferric maltol | 100 | 30 mg/30 mg |

Lower amounts of iron can be given and produce similar results with better tolerability. Hepicidin, a protein that regulates iron absorption, may play a role in oral iron dosing. A large dose of iron in the morning may elevate hepicidin levels and prevent further iron absorption of subsequent doses for at least the rest of the day, potentially up to 48 hours later.[25] Furthermore, once daily dosing of iron may result in a lower amount of iron being absorbed versus every other day dosing.[26] These studies have led some to propose that oral iron could be dosed every other day, particularly if the patient has difficulty tolerating a larger daily dose of oral iron. However, no long-term studies have been conducted to support this dosing strategy.

Adverse drug reactions to therapeutic doses of iron are primarily GI in nature and consist of dark discoloration of feces, constipation or diarrhea, nausea, and vomiting. GI effects usually are common, dose-related, and are similar among iron salts when equivalent amounts of elemental iron are administered. Administration of smaller amounts of iron with each dose or administration with meals may minimize these adverse effects. Histamine-2 blockers or proton-pump inhibitors reduce gastric acidity and may impair iron absorption. Table 122-2 lists important drug interactions with iron.

TABLE 122-2

**Iron Salt-Drug Interactions**

| Drugs That Decrease Iron Absorption | Drugs Affected by Iron |
|---|---|
| $Al^-$, $Mg^-$, and $Ca^{2+}$-containing antacids<br>Tetracycline and doxycycline<br>$Histamine_2$ antagonists<br>Proton-pump inhibitors<br>Cholestyramine | Levodopa ↓ (chelates with iron)<br>Methyldopa ↓ (decreases efficacy of methyldopa)<br>Levothyroxine ↓ (decreased efficacy of levothyroxine)<br>Penicillamine ↓ (chelates with iron)<br>Fluoroquinolones ↓ (forms ferric ion quinolone complex)<br>Tetracycline and doxycycline ↓ (when administered within 2 hours of iron salt) |

Failure to respond to iron treatment regimens necessitates reevaluation of the patient's condition. Common causes of treatment failure include poor patient adherence, inability to absorb iron, incorrect diagnosis, continued bleeding, or a concurrent inflammatory condition that impairs a full response. Even when iron deficiency is present, response may be impaired when a coexisting cause for anemia exists. Rarely a patient has diminished ability to absorb iron, most often due to previous gastrectomy, such as gastric bypass surgery, or celiac disease. Regardless of the form of oral therapy used, treatment should continue for 3 to 6 months after the anemia is resolved to allow for repletion of iron stores and to prevent relapse. Patients should be instructed to store oral iron out of reach of children and pets as small amounts can result in a fatal overdose. Treatment for acute iron poisoning is discussed in Chapter e8, "Clinical Toxicology."

### Parenteral Iron Therapy

Indications for parenteral iron therapy include intolerance to oral, malabsorption, and nonadherence. Patients with significant blood loss who refuse transfusions and cannot take oral iron therapy also may require parenteral iron therapy. Parenteral iron therapy should also be considered, possibly first line, in patients with inflammatory bowel disease and those with gastric bypass/gastric resection due to poor oral absorption.[27] Parenteral iron therapy is also used for patients with chronic kidney disease (see Chapter 63), especially those undergoing hemodialysis, and for some cancer patients receiving chemotherapy on erythropoiesis-stimulating agents (ESAs; Chapter 150). Seven different parenteral iron preparations available in the United States are low molecular weight iron dextran, ferric gluconate, iron sucrose, ferumoxytol, ferric derisomaltose, ferric pyrophosphate citrate, and ferric carboxymaltose (Table 63-4). They differ in their molecular size, pharmacokinetics, bioavailability, and adverse effect profiles. Although toxicity profiles of these agents differ, clinical studies indicate that each is efficacious. High molecular weight iron dextran parenteral preparations have been previously associated with more anaphylactic reactions. The high molecular weight product is no longer available. The low molecular weight has a lower risk of these reactions, but it requires a test dose prior to full dose administration. Fatal reactions have also occurred in patients who tolerated the test dose with the high molecular weight product. The safety profile of parenteral iron is largely assessed by spontaneous reports to the FDA and observational studies. All parenteral iron preparations carry a risk for anaphylactic reactions but the risk is lower than that for high molecular weight iron dextran.[28,29] The FDA recommends that resuscitation equipment and trained staff be available during administration of all iron dextran preparations. A concern with parenteral iron is that iron may be released too quickly and overload the ability of transferrin to bind it, leading to free iron reactions that can interfere with neutrophil function.

Iron dextran, a complex of $Fe^{3+}$ hydroxide and the carbohydrate dextran, contains 50 mg of iron/mL and can be given via the intramuscular or IV route. Different brands of iron dextran are available and differ in their molecular weight. They are not interchangeable. The intramuscular route is no longer used routinely and requires Z-tract injection technique.[30] Methods of IV administration include multiple injections or an infusion of a diluted preparation. This latter method often is referred to as total dose infusion.

Total replacement doses of IV iron dextran can be given as a single dose, but this method of administration is not FDA-approved. A test dose is still required. Patients who receive total dose infusions are at higher risk for adverse drug reactions, such as arthralgias, myalgias, flushing, malaise, and fever. Patients with preexisting immune-mediated diseases, such as active rheumatoid arthritis or systemic lupus erythematosus, are at high risk for adverse drug reactions because of their hyperreactive immune response.[31]

Ferric gluconate is a complex of iron bound to one gluconate and four sucrose molecules in a repeating pattern. Ferric gluconate is available in an aqueous solution. No direct transfer of iron from the $Fe^{3+}$ gluconate to transferrin occurs. The complex is taken up quickly by the mononuclear phagocytic system and has a half-life of about 1 hour in the bloodstream. Ferric gluconate produces fewer anaphylactic reactions than iron dextran does. Adverse drug reactions of sodium ferric gluconate include cramps, nausea, vomiting, flushing, hypotension, intense upper gastric pain, rash, and pruritus.[32]

Iron sucrose is a polynuclear iron (III) hydroxide in sucrose complex. Following IV administration of iron sucrose, the iron is released directly from the circulating iron sucrose to transferrin and is taken up by the mononuclear phagocytic system and metabolized. The half-life is about 6 hours, with a volume of distribution similar to that of iron dextran.[33] Adverse drug reactions include leg cramps and hypotension.

Ferumoxytol is FDA-approved to treat iron deficiency in adults with chronic kidney disease and adults with IDA who have not responded to oral iron. No test dose is required but anaphylaxis can occur and patients should be observed for at least 30 minutes after each dose. A warning was added in 2015 due to case reports of fatal and nonfatal anaphylactic reactions to the product. It should not be used in patients who previously had an allergic reaction to other iron preparations. Ferumoxytol can also interfere with magnetic resonance imaging (MRI) scans and the radiologist should be notified if the patient has received this medication within 3 months of the scan.[34]

Ferric carboxymaltose received approval for treatment of IDA in those who have failed oral iron therapy or who have intolerance to oral therapy. The approval of this product was delayed due to hypophosphatemia seen in clinical trials. No additional warnings were required and no clinical issues related to hypophosphatemia have been reported. This product can also be given in a two-dose regimen or a single-dose regimen. It is also approved for chronic kidney disease patients not on hemodialysis.[35]

Ferric derisomaltose is approved for patients with IDA who have intolerance to oral iron or an unsatisfactory response to oral iron, as well as patients with chronic kidney disease who do not depend on hemodialysis. This product can be given as a single- or multi-dose regimen.

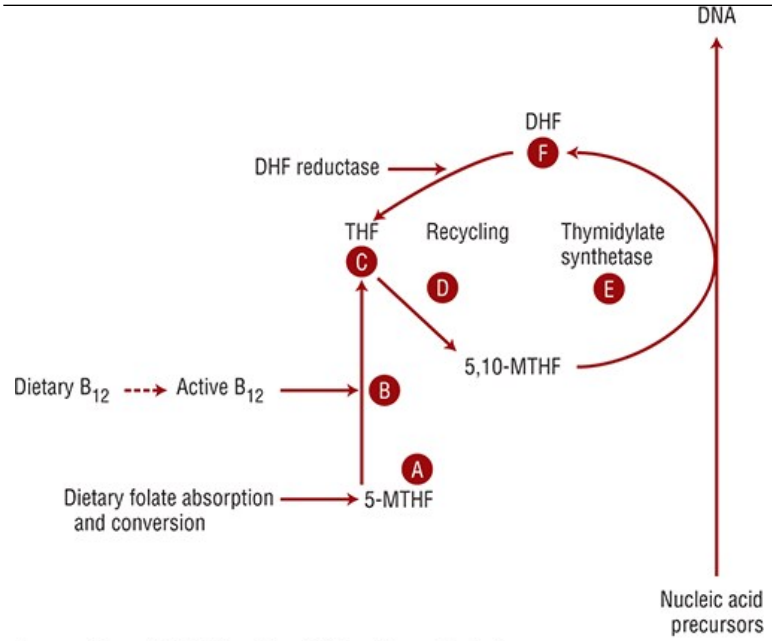
Increased risk for infection is a concern with parenteral iron preparations because iron is a growth factor for some bacteria, but a meta-analysis reported that IV iron does not increase the risk for infection.[36] Parenteral iron products are discussed in more detail in Chapter 63.

## MEGALOBLASTIC ANEMIAS

Macrocytic anemias are divided into megaloblastic and nonmegaloblastic anemias. Macrocytosis, as seen in megaloblastic anemias, is caused by abnormal DNA metabolism resulting from vitamin $B_{12}$ or folate deficiency. It can also be caused by administration of various drugs, such as hydroxyurea, zidovudine, cytarabine, methotrexate, azathioprine, 6-mercaptopurine, and cladribine. In vitamin $B_{12}$– or folate-deficiency anemia, megaloblastosis results from interference with folic acid- and vitamin $B_{12}$–interdependent nucleic acid synthesis in the immature erythrocyte (Fig. 122-6).

**FIGURE 122-6**

Drug-induced megaloblastosis.




Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*


Although vitamin $B_{12}$ and folate deficiency are common causes of macrocytosis, other possible causes must be considered if these deficiencies are not found. These can include aplastic anemia, myelodysplastic syndromes, alcohol abuse, and multiple myeloma. Macrocytosis is the most typical morphologic abnormality associated with excessive alcohol consumption. Even with adequate folate and vitamin $B_{12}$ levels and the absence of liver disease, patients with high alcohol intake may present with an alcohol-induced macrocytosis. Cessation of alcohol ingestion resolves the macrocytosis within a couple of months.

## Vitamin $B_{12}$–Deficiency Anemia

The exact prevalence of vitamin $B_{12}$–deficiency anemia in the United States is unknown. Risk increases with age.[37] One study conducted in the United States and the United Kingdom found that the prevalence of vitamin $B_{12}$ deficiency increased from about 6% in adults younger than 60 years to 20% in those older than 60 years.[38] Gastric acid–suppressing agents may inhibit cobalamin release from food, and their use is associated with an increased risk. Older adults in the United States have a high prevalence (up to 15%) of elevated MMA levels and associated low or low-normal vitamin $B_{12}$ levels, likely due to atrophic gastritis and malabsorption of food-bound vitamin $B_{12}$.[37]

### Etiology

4 The three major causes of vitamin $B_{12}$ deficiency are inadequate intake, malabsorption syndromes, and inadequate utilization. Inadequate dietary consumption of vitamin $B_{12}$ is rare. It usually occurs only in patients who are strict vegans without supplementation, chronic alcoholics, and older adults who consume a "tea and toast" diet because of financial limitations or poor dentition. Decreased vitamin $B_{12}$ absorption can occur with loss of intrinsic factor by autoimmune mechanisms (such as pernicious anemia, in which gastric parietal cells are selectively damaged), chronic atrophic gastritis, or stomach surgery. One of the most frequent causes of low serum $B_{12}$ levels results from the inability of vitamin $B_{12}$ to be cleaved and released from proteins in food because of inadequate gastric acid production. Treatment of *Helicobacter pylori* may improve vitamin $B_{12}$ status because this bacterial infection is a cause of chronic gastritis.[39] Vitamin $B_{12}$ deficiency may occasionally result from overgrowth of bacteria in the bowel that uses vitamin $B_{12}$ or from injury or removal (from Crohn's disease or small bowel surgery, respectively) of ileal receptor sites where vitamin $B_{12}$ and the intrinsic factor complex are absorbed. Blind loop syndrome, Whipple disease, Zollinger–Ellison syndrome, tapeworm infestations, intestinal

resections, tropical sprue, surgical resection of the ileus, pancreatic insufficiency, inflammatory bowel disease, advanced liver disease, tuberculosis, and Crohn's disease may contribute to the development of vitamin $B_{12}$ deficiency.[37] Metformin may reversibly decrease $B_{12}$ absorption, likely due to its effects on the intestinal mucosa in the ileum and calcium homeostasis. Low $B_{12}$ related to metformin can occur within months of starting the medication, but it is more likely after 5 years and some clinicians will monitor $B_{12}$ in patients receiving long-term metformin therapy or those with a poor oral intake of vitamin $B_{12}$.[40] Proton pump inhibitors and histamine-2 receptor antagonists may also contribute to vitamin $B_{12}$ deficiency because an acidic environment is needed for vitamin $B_{12}$ to be absorbed in the GI tract from food.[41] Long-term use of these agents for 2 or more years increases the risk of deficiency.[41]

### Pathophysiology

Vitamin $B_{12}$ works closely with folate in the synthesis of building blocks for DNA and RNA, is essential in maintaining the integrity of the neurologic system, and plays a role in fatty acid biosynthesis and energy production. It is a water-soluble vitamin obtained exogenously by ingestion of meat, fish, poultry, dairy products, and fortified cereals. The body stores several years of vitamin $B_{12}$, of which about 50% is in the liver. The recommended daily allowance is 2 µg in adults and 2.6 µg in pregnant or breast-feeding women. The average Western diet provides 5 to 15 µg of vitamin $B_{12}$ daily, of which 1 to 5 µg is absorbed.[37] Vitamin $B_{12}$ deficiency can take several years to develop following vitamin deprivation.

Once dietary cobalamin enters the stomach, pepsin and hydrochloric acid release the cobalamin from animal proteins. The cobalamin then binds with intrinsic factor that serves as a cell-directed carrier protein similar to transferrin for iron. This complex attaches to mucosal cell receptors in the distal ileum, the intrinsic factor is discarded, and the cobalamin is bound to transport proteins (transcobalamin I, II, and III). Passive diffusion is an alternate pathway for vitamin $B_{12}$ absorption independent of intrinsic factor or an intact terminal ileum and accounts for about 1% of vitamin $B_{12}$ absorption.[37]

Vitamin $B_{12}$ deficiency can cause neurologic and hematologic complications. They usually start with bilateral paraesthesia in the extremities; deficits in proprioception and vibration can also be present. If not treated, this can progress to ataxia, dementia-like symptoms, psychosis, and vision loss. In children, prolonged deficiency can lead to poor brain development.[14,42] Patients with unexplained neuropathies should be evaluated for vitamin $B_{12}$ deficiency.

### Laboratory Findings

In macrocytic anemias, MCV is elevated, but some patients deficient in vitamin $B_{12}$ may have a normal MCV. If there is a coexisting cause of microcytosis, the MCV may not be elevated.[36] A peripheral blood smear shows macrocytosis accompanied by hypersegmented polymorphonuclear leukocytes (one of the earliest and most specific indications of this disease), oval macrocytes, anisocytosis, and poikilocytosis. Serum lactate dehydrogenase and indirect bilirubin levels may be elevated as a result of hemolysis or ineffective erythropoiesis.[14] Other laboratory findings include a low reticulocyte count, low serum vitamin $B_{12}$ level (less than 200 pg/mL [148 pmol/L]), and low Hct.

In the early stages of vitamin $B_{12}$ deficiency, classic signs and symptoms of megaloblastic anemia may not be evident, and serum levels of vitamin $B_{12}$ may be within normal limits or borderline low (200-300 pg/mL [148-221 pmol/L]). Therefore, measurement of MMA and homocysteine may be useful because these parameters are typically the first to change. Because MMA and homocysteine are involved in enzymatic reactions that depend on vitamin $B_{12}$, vitamin $B_{12}$ deficiency leads to accumulation of these metabolites. Elevations in MMA are more specific for vitamin $B_{12}$ deficiency. Homocysteine is also elevated in several other situations including folate deficiency, chronic renal disease, alcoholism, smoking, and use of steroid or cyclosporine therapy.[42]

Blood levels of vitamin $B_{12}$ should be drawn for all patients with suspected vitamin $B_{12}$ deficiency. Vitamin $B_{12}$ values less than 200 pg/mL (148 pmol/L) are diagnostic for $B_{12}$ deficiency. Subclinical vitamin $B_{12}$ deficiency is sometimes found with vitamin $B_{12}$ levels of 200 to 300 pg/mL (148-221 pmol/L).[43] Some patients with clinical $B_{12}$ deficiency manifesting as neurological disease have normal hematological parameters.

The Schilling test was once performed to determine whether replacement of vitamin $B_{12}$ should occur via an oral or parenteral route due to pernicious anemia, but evidence now shows that oral replacement is as efficacious as parenteral supplementation because of the vitamin $B_{12}$ absorption pathway independent of intrinsic factor.[37,44]

### Treatment

Early treatment is important because neurologic damage may be irreversible if the deficiency is not detected and corrected within months. In addition to replacement therapy, any underlying etiology that is treatable, such as bacterial overgrowth, should be corrected. Indications for starting oral or parenteral therapy include megaloblastic anemia or other hematologic abnormalities and neurologic disease from deficiency.[42] Those with borderline low levels of $B_{12}$ but no hematologic abnormalities should be followed at yearly intervals; monitoring MMA and homocysteine may also be useful.[42] Patients should be counseled on the types of foods high in vitamin $B_{12}$ content such as fortified cereals, fish, animal liver, milk, clams, and yogurt. Oral vitamin $B_{12}$ replacement is indicated for those without neurologic complications or significant symptoms and can be used effectively to treat pernicious anemia because of passive absorption, independent of intrinsic factor.[15] Cyanocobalamin is used primarily in the United States while hydroxycobolamin may be used in other countries. The typical dose for oral therapy is cyanocobalamin 1,000 µg once daily. Higher doses of (1,000-2,000 µg) of vitamin $B_{12}$ may be given to patients with malabsorption and is as effective as intramuscular administration in achieving hematologic and neurologic responses.[37,44] If vitamin $B_{12}$ levels are marginally low and either MMA or both MMA and homocysteine levels are elevated, oral administration of 1,000 µg of vitamin $B_{12}$ daily should be strongly considered.[45] Timed-release preparations of oral cobalamin should be avoided.[46] Nonprescription 1,000 µg cobalamin tablets are available, among several other strengths at a low cost. Oral replacement may be as effective as parenteral administration in achieving hematologic and neurologic responses.[37,38] However, parenteral therapy is usually given if patients have neurologic or severe anemia symptoms to protect against further progression. A commonly used initial parenteral vitamin $B_{12}$ regimen consists of daily intramuscular or deep subcutaneous injections of 1,000 µg of cyanocobalamin for 1 week to saturate vitamin $B_{12}$ stores in the body and resolve clinical manifestations of the deficiency. After that, it can be given weekly for 1 month and monthly thereafter for maintenance. The series of daily parenteral injections may be omitted if administration is difficult or inconvenient. In this case, the parenteral injection is then given weekly, sometimes for longer than 1 month. Patients can be instructed to give these injections at home to avoid the cost of an office visit and convenience. After symptoms have resolved and hematologic indices and vitamin $B_{12}$ levels have normalized, patients can be converted from parenteral therapy to oral maintenance therapy.[47] When patients are converted from the parenteral to the oral form of cobalamin, oral cobalamin daily can be initiated on the due date of the next injection. Vitamin $B_{12}$ should be continued for life in patients with pernicious anemia.

In addition to the oral and parenteral forms, vitamin $B_{12}$ is available as a nasal spray for patients in remission following intramuscular vitamin $B_{12}$ therapy who have no neurologic involvement. The nasal spray is administered once weekly. Intranasal administration should be avoided for patients with nasal diseases or those receiving medications intranasally in the same nostril. Patients should not administer the spray 1 hour before or after ingestion of hot foods or beverages, which can impair cobalamin absorption. The efficacy of the nasal spray formulation has not been well studied and may have variable absorption. It should be used for maintenance therapy only after hematologic parameters have normalized.

Potential adverse drug reactions with vitamin $B_{12}$ replacement therapy are rare. Uncommon adverse drug reactions are headache, weakness, and hypokalemia.

## Folic Acid Deficiency Anemia

### Epidemiology

Folic acid deficiency is one of the most common vitamin deficiencies occurring in the United States, largely because of its association with excessive alcohol intake and pregnancy. Fortification of grain products in the 1990s increased folate intake across the United States. According to data from the National Health and Nutrition Examination Survey (NHANES), most people in the United States intake adequate dietary amounts of folate and only 0.5% of children aged 1 to 18 years have folate deficiency.[48]

## Etiology

Major causes of folic acid deficiency include inadequate intake, decreased absorption, and increased folate requirements. Poor eating habits make this deficiency more common in older adults, teenagers whose diets consist of "junk food," and individuals with alcoholism, food insecurity, chronic illness, or dementia. Folic acid absorption may decrease for patients who have malabsorption syndromes or received certain drugs. In patients with alcoholism with poor dietary habits, alcohol interferes with folic acid absorption and utilization at the cellular level and decreases hepatic stores of folic acid.

Increased folate requirements may occur when the rate of cellular division is increased, as seen in pregnant women; patients with hemolytic anemia, malignancy, chronic inflammatory disorders such as Crohn's disease, rheumatoid arthritis, or psoriasis; patients undergoing long-term dialysis; burn patients; and adolescents and infants during their growth spurts. This hyperutilization eventually can lead to anemia, particularly when the daily intake of folate is borderline, resulting in inadequate replacement of folate stores.

Several drugs have been reported to cause a folic acid deficiency. Some drugs (eg, azathioprine, 6-mercaptopurine, 5-fluorouracil, hydroxyurea, and zidovudine) directly inhibit DNA synthesis. Other drugs are folate antagonists and inhibit dihydrofolate reductase; the most toxic is methotrexate (other examples include pentamidine, trimethoprim, and triamterene). A number of drugs (eg, phenytoin, carbamazepine, valproate, primidone) antagonize folate via poorly understood mechanisms but are thought to reduce vitamin absorption by the intestine (see Chapter e125). Since folic acid doses as low as 1 mg/day may affect serum phenytoin levels, routine folic acid supplementation is not generally recommended.[42] Alcohol can also interfere with folic acid absorption, likely through its effects on the intestinal mucosa.[41]

## Pathophysiology

Folic acid is a water-soluble vitamin readily destroyed by cooking or processing. It is necessary for the production of DNA and RNA. It acts as a methyl donor to form methylcobalamin, which is used in the remethylation of homocysteine to methionine. Because humans are unable to synthesize sufficient folate to meet total daily requirements, they depend on dietary sources. Major dietary sources of folate include fresh, green leafy vegetables, citrus fruits, yeast, mushrooms, dairy products, and animal organs such as liver and kidney. Once absorbed, dietary folate must be converted to the active form tetrahydrofolate through a cobalamin-dependent reaction. In 1997, the United States mandated that grain products be fortified with folic acid to increase the dietary intake of folate. This amount of supplementation was chosen to decrease the incidence of neural tube defects without masking occult vitamin $B_{12}$ deficiency.

As a result of grain product fortification, neural tube defect frequency has decreased by 25% to 30%.[49] Although body demands for folate are high because of high rates of RBC synthesis and turnover, the minimum daily requirement is 50 to 100 µg. In the general population, the recommended daily allowance for folate is 400 µg in nonpregnant females, 600 µg in pregnant females, and 500 µg in lactating females.[45] Because the body stores about 15 to 30 mg of folate, primarily in the liver, cessation of dietary folate intake can result in deficiency in months.[50]

## Laboratory Findings

It is critically important to rule out vitamin $B_{12}$ deficiency when folate deficiency is suspected to prevent neurologic complications developing from vitamin $B_{12}$ deficiency. Laboratory changes associated with folate deficiency are similar to those seen in vitamin $B_{12}$ deficiency, except serum vitamin $B_{12}$ and MMA levels are normal. Serum folate levels less than 2 ng/mL (4.5 nmol/L) are considered low, although normal ranges may vary between institutions. The RBC folate level (less than 150 ng/mL [340 nmol/L]) also declines, and levels remain constant throughout the life span of the erythrocyte.[11] The RBC folate levels may not provide additional information beyond the serum folate level. If serum or erythrocyte folate levels are borderline, serum homocysteine usually is increased with a folic acid deficiency. If serum MMA levels also are elevated, vitamin $B_{12}$ deficiency must be ruled out given that folate does not participate in MMA metabolism.

## Treatment

Therapy for folic acid deficiency consists of administration of exogenous folic acid to normalize hematologic labs, replace body stores, and resolve signs and symptoms. In most cases, 1 mg daily is sufficient to replace stores; doses of 1 to 5 mg daily may be necessary in cases of deficiency due to

malabsorption. Parenteral folic acid is available but rarely necessary. Synthetic folic acid is almost completely absorbed by the GI tract and is converted to tetrahydrofolate without cobalamin. Therapy should continue for about 4 months if the underlying cause of the deficiency can be identified and corrected to allow for clearance of all folate-deficient RBCs from the circulation. Examples of foods high in folic acid include beef liver, fortified cereals, lentils, green leafy vegetables, orange juice, and rice. They should be encouraged in the diet. Long-term folate administration may be necessary in patients with chronic conditions associated with increased folate requirements. Low-dose folate therapy (500 µg daily) can be administered when anticonvulsant drugs produce a megaloblastic anemia so that discontinuation of anticonvulsant therapy may not be necessary. Adverse drug reactions have not been reported with folic acid doses used for replacement therapy. It is considered nontoxic at high doses and is rapidly excreted in the urine.

Although megaloblastic anemia during pregnancy is rare, the most common cause is folate deficiency. Periconceptional folic acid supplementation is recommended to decrease the occurrence and recurrence of neural tube defects (eg, anencephaly and spinal bifida). Folic acid supplementation at a dose of 400 µg daily is recommended for all women. Women who have previously given birth to offspring with neural tube defects or those with a family history of neural tube defects should ingest 1 to 4 mg daily of folic acid.[49,51,52] Higher levels of folic acid supplementation should not be attained via ingestion of excess multivitamins because of the risk of fat-soluble vitamin toxicity.[52] Prenatal vitamins usually have a higher amount of folic acid as compared with general multivitamins to ensure adequate supplementation is attained. It is essential that women in their childbearing years maintain adequate folic acid intake.

## ANEMIA OF INFLAMMATION

### Epidemiology

AI is a term used to describe both ACD and anemia of critical illness. This term was developed to reflect the inflammatory process resulting in disturbances in iron homeostatis underlying both types of anemia. The onset of anemia of critical illness is rapid, generally over days, and often occurs in a hospital setting due to tissue damage and acute inflammatory changes. ACD has a similar mechanism, but develops over months to years from an underlying chronic condition. Globally, AI is one of the most common forms of anemia, particularly among older adults, although its prevalence is not known due to the complex and multifaceted nature of the disease. ACD is associated with common disease states that may mimic the symptoms of anemia, which causes the diagnosis of ACD to be sometimes overlooked in the outpatient setting. Anemia of critical illness is a common complication in critically ill patients and is found almost universally in this patient population.[53]

### Etiology

AI is an anemia traditionally associated with infectious or inflammatory processes, tissue injury, and conditions associated with the release of proinflammatory cytokines. The etiology of AI can be multifactorial and the diagnosis is usually one of exclusion. A comprehensive history of the illness is important to help rule out other potential causes of anemia. Although it may be difficult to delineate between IDA and AI, it is important to exclude IDA as the true or competing etiology. Various conditions associated with ACD may predispose patients to blood loss (malignancy, GI blood loss from treatments with aspirin, NSAIDs, or corticosteroids). ACD is often observed in patients with diseases containing an inflammatory component lasting longer than 1 to 2 months, although it can occur in conditions with a more rapid onset of several weeks, such as pneumonia. Anemia associated with human immunodeficiency virus (HIV), autoimmune conditions, cancer, and heart failure are common forms of AI. The degree of anemia in ACD generally reflects the severity of the underlying disease.

Factors that contribute to anemia in critically ill patients include sepsis, frequent blood sampling, surgical blood loss, immune-mediated functional iron deficiency, decreased production of endogenous EPO, reduced RBC life span, and active bleeding, especially in the GI tract. A combination of these factors often exists, creating a rapid anemic state over days. Additional comorbid factors include coagulopathies and nutritional deficits such as poor oral intake and altered absorption of vitamins and minerals, including iron, vitamin $B_{12}$, and folate.[54] Deleterious effects of anemia include an increased risk of cardiac-related morbidity and mortality, especially for patients with known cardiovascular disease. Persistent tissue hypoxia can result in cerebral ischemia, myocardial ischemia, multiple organ deterioration, lactic acidosis, and death. The consequences of anemia in critically ill patients may be enhanced because of the increased metabolic demands of critical illness. Weaning anemic patients from mechanical ventilation may be more difficult, as low Hg has been identified as a potential risk factor for poor outcomes.[55,56] This is likely due to Hg's critical role in oxygen delivery; low Hg has been associated with increased work of breathing and cardiac output.[57-59]

## Pathophysiology

AI is a hypoproliferative response to stimulation of the cellular immune system by various underlying disease processes. The pathogenesis of AI is multifactorial and is characterized by a blunted EPO response to anemia, an impaired proliferation of erythroid progenitor cells, and a disturbance of iron homeostasis. Increased iron uptake and retention occur within cells. The RBCs have a shortened life span, and the bone marrow's capacity to respond to EPO is inadequate to maintain normal Hb concentration. The cause of this defect is uncertain but related to impaired release of iron from bone marrow cells. Iron availability to erythroid progenitor cells is therefore limited. Various cytokines, such as interleukin-1, interferon-γ, interleukin-6, and tumor necrosis factor released during illness, may inhibit the production or action of EPO or the production of RBCs.[60] These cytokines also upregulate hepcidin, a small peptide that regulates iron availability. Increased hepcidin inhibits iron absorption from the gastrointestinal tract and prevents release from macrophages which are elevated during inflammation. Inflammation also increases the uptake of iron by macrophages reducing free iron for erythropoiesis.[60,61]

## Laboratory Findings

ACD tends to be a mild (Hb greater than 9.5 g/dL [95 g/L; 5.90 mmol/L]) or moderate (Hb greater than 8 g/dL [80 g/L; 4.97 mmol/L]) anemia.[60] No definitive test can confirm the diagnosis of AI. The clinician should maintain a high index of suspicion for any patient with a chronic inflammatory or neoplastic disease. AI may coexist with IDA and folic acid deficiency because many patients with these conditions have poor dietary intake. Examination of the bone marrow, although not routinely performed, reveals an abundance of iron, suggesting that the release mechanism for iron is the central defect. Patients with AI usually have a decreased serum iron level, but unlike patients with IDA, their TIBC is decreased and their serum ferritin level is normal or increased. Ferritin is an acute phase reactant and is often elevated during inflammation, helping to delineate AI from IDA. Transferrin saturation is typically decreased. AI usually is normocytic and normochromic with mildly depressed Hb. Patients with concurrent AI and IDA usually have microcytes and a more severe anemia. Table 122-3 shows lab values seen in AI and IDA. Erythrocyte survival may be reduced for patients with AI, but a compensatory erythropoietic response does not occur. A low reticulocyte count indicates underproduction of RBCs.[60] As discussed in the IDA section, hepcidin levels are not routinely used for diagnosis but would likely be elevated in a patient with ACD.[62]

TABLE 122-3

**Laboratory Value Differences Between Anemia of Inflammation and Iron-Deficiency Anemia**

| | Anemia of Inflammation | Iron-Deficiency Anemia |
|---|---|---|
| Iron | ↓ | ↓ |
| Transferrin | ↓ or NL | ↑ |
| Transferrin saturation | ↓ | ↓ |
| Ferritin | ↑ or NL | ↓ |
| Soluble transferrin receptor | NL | ↑ |

NL, normal limits.

## Treatment

Treatment of AI depends on the underlying etiology. Resolution of the underlying condition may prompt recovery from anemia. Guidelines exist for management of anemia in patients with cancer or chronic kidney disease. Although the goals of therapy should include treating the underlying disorder and correcting reversible causes of anemia, accomplishment of these goals may not be feasible nor completely reverse hematologic and physiologic abnormalities. If AI is mild and does not affect the patient's quality of life or progression of other disease states, additional therapy may not

be needed.

Iron supplementation is effective only if iron deficiency is present and should not be utilized for AI in its absence. During inflammation, oral or parenteral iron therapy may not be as effective. Absorption is impaired because of downregulation of ferroportin and iron diversion mediated by cytokines.[60] Because iron is a required nutrient for proliferating microorganisms, supplementation may also theoretically increase the risk of infections. Therefore, iron therapy should be reserved for patients with an established iron deficiency.[60]

ESAs have been used to stimulate erythropoiesis for patients with symptomatic AI since a relative EPO deficiency exists in comparison to the degree of anemia. Similar to endogenous EPO, response to exogenous ESA may be blunted in AI. Two agents are available: recombinant epoetin alfa and recombinant darbepoetin alfa. Although both agents share the same mechanism of action, darbepoetin alfa has a longer half-life and can be administered less frequently. ESAs are FDA-approved for AI due to chronic kidney disease and HIV infection, as well as anemia due to malignancy, but are sometimes used off label for AI due to other underlying causes. The initial dosages of epoetin alfa and darbepoetin alfa are 50 to 100 Units/kg three times per week and 0.45 µg/kg once weekly, respectively. Response to ESAs varies depending on dose and cause of the anemia. Higher doses may be required to overcome hyporesponsiveness. Since ESAs are more effective when the marrow has an adequate supply of iron, cobalamin, and folic acid, these agents should be used in combination with iron therapy.

Iron deficiency can occur in patients treated with ESAs, so close monitoring of iron levels is necessary. Some patients develop “functional” iron deficiency, in which the iron stores are normal but the supply of iron to the erythroid marrow is less than necessary to support the demand for RBC production. Therefore, many practitioners routinely supplement ESA therapy with oral or IV iron therapy to maintain a serum ferritin ≥100 ng/mL (mcg/L; 225 pmol/L) or serum transferrin saturation (TSAT) ≥20%. Potential toxicities of exogenous ESA administration include increases in blood pressure, nausea, headache, fever, bone pain, and fatigue. Less-common adverse drug reactions include seizures, thrombotic events, and allergic reactions such as rashes and local reactions at the injection site. Tumor progression with these agents can also occur and is discussed in Chapter 150. Further discussion of dosing guidelines and potential adverse outcomes of ESA treatment in populations for which treatment is FDA-approved are discussed in Chapters 63 and 150. If ESAs are used, the practitioner must monitor to ensure the patient’s Hb does not exceed 12 g/dL (120 g/L; 7.45 mmol/L) with treatment or that Hb does not rise greater than 1 g/dL (10 g/L; 0.62 mmol/L) every 2 weeks since both of these events have been associated with increased mortality and cardiovascular events.[63] Continued monitoring of Hb should be considered every 2 to 4 weeks thereafter. If no rise in Hb is seen after 8 weeks of optimal therapy, the patient should be considered EAS nonresponsive and therapy may be discontinued.

Transfusions of packed red blood cells are effective but should be limited to situations in which oxygen transport is inadequate due to concomitant medical problems and symptomatic patients with insufficient time to respond to other methods. RBC transfusions should be strongly considered for severe AI with complications involving bleeding. Liberal use of transfusions to correct anemia in critical illness can result in adverse patient outcomes.[53] Transfusion risks may include transmission of blood-borne infections, development of autoantibodies, transfusion reactions, and iron overload. Transfusions begin to be considered in most situations for those with severe anemia (Hb less than 7-8 g/dL [70-80 g/L; 4.34-4.97 mmol/L]).[64]

Critically ill patients require the necessary substrates of iron, folic acid, and vitamin $B_{12}$ for RBC production. Parenteral iron is generally preferred in this population because patients often are undergoing enteral therapy or because of concerns regarding inadequate iron absorption. The disadvantage of parenteral therapy is the theoretical risk of infection, hypersensitivity reactions, including anaphylaxis, and hypotension during infusion.

ESAs have been used to treat the anemia of critical illness, but they are not FDA-approved for this indication. In critically ill patients, the use of ESAs did not significantly reduce mortality or length of ICU stay.[65] The few randomized controlled trials which evaluated ESAs in this patient population did not consistently show a decrease in transfusion requirements in ESA-treated patients.[66] Additionally, their use is often limited by the rapid progression of anemia in this setting and the increased risk of thrombotic events with their use. Further investigation is necessary to determine the effectiveness of ESAs in critically ill patients.

Many critically ill patients receive RBC transfusions despite the inherent risks associated with transfusions. Stored RBCs may not function as well as endogenous blood. Although RBC transfusions may increase oxygen delivery to tissues, cellular oxygen may not increase.[67] Transfusion practices in ICUs vary, and clinicians use different Hb concentrations as thresholds for administering transfusions. The decision to use transfusions must consider the risks, including transmission of infections; volume overload, especially for patients with renal or heart failure; iron overload; and immune-mediated reactions such as febrile reactions, hemolysis, and anaphylaxis. The clinician also must consider administrative, logistic, and economic

factors, including the shortage of blood supplies.

The recognition of hepcidin in the regulation of iron homeostasis and its role in ACD has led to interest in new agents targeted at hepcidin. Mechanisms for these novel agents include inhibition of hepcidin production, circulating hepcidin, or hepcidin-inducing cytokines, including interleukin-6.

Prolyl hydroxylases have become potential targets for AI because they regulate hypoxia-inducible factors, which increase endogenous EPO formation and iron delivery. Prolyl hydroxylase inhibitors are in clinical trials to treat anemia in patients on hemodialysis.

## ANEMIA IN OLDER ADULTS

### Epidemiology

Anemia is one of the most common clinical problems observed in older adults, with about 20% of people aged 85 years and older affected.[68] Older patients with the highest incidence of anemia are those who are hospitalized, followed by residents of nursing homes and other institutions, with an estimated rate of 31% to 40%.[69] Although anemia is common in older adults, it should not be regarded as an inevitable outcome of aging. The body's set point of Hb does not fall with age. An underlying cause can be identified in about two-thirds of older patients. Undiagnosed and untreated anemia has been associated with adverse outcomes, including all-cause hospitalization, hospitalization secondary to cardiovascular disease, and all-cause mortality.[70] Anemia is an independent predictor of death and major clinical adverse events in older adults with stable symptomatic coronary artery disease.[71] Anemia can exacerbate neurologic and cognitive conditions and can adversely influence quality of life and physical performance in older adults.[72] Anemia may be an indication of serious diseases such as cancer.

### Pathophysiology

Aging is associated with a progressive reduction in hematopoietic reserve, which increases the risk of anemia in times of hematopoietic stress.[73] Dysregulation of proinflammatory cytokines, most notably interleukin-6, may inhibit EPO production or interact with EPO receptors.[74] Although Hb levels may remain normal, the diminished marrow reserve leaves older adults more susceptible to other causes of anemia. Renal insufficiency, which also is common in older adults, may reduce the ability of the kidneys to produce EPO. Older patients often have a normal creatinine level but a diminished glomerular filtration rate. Myelodysplastic syndromes are another common cause of anemia in older adults, but most anemia cases in older adults are multifactorial.

### Etiology

In the acute care setting, the most common causes of anemia in older adults are chronic disease (35%), unexplained (17%), and iron deficiency (15%), whereas in community-based outpatient clinics, the most common causes are unexplained (36%), infection (23%), and chronic disease (17%).[75] Another common problem in older adults is vitamin $B_{12}$ deficiency. The most common causes of clinically overt vitamin $B_{12}$ deficiency are food or cobalamin malabsorption (more than 60% of cases) and pernicious anemia (15%-20% of cases).[76]

One often overlooked major factor that may contribute to anemia in the older population is nutritional status. Cognitive and functional impairments in the older population may create barriers for patients to obtain and prepare a nutritious diet. Nutritional deficiencies that are not severe enough to affect the hematopoietic system in the younger population may contribute to anemia in older adults. Edentulous or older adults who may be too ill to prepare their meals are at risk for nutritional folate deficiency. Risk factors for inadequate folate intake in older adults include low caloric intake, inadequate consumption of fortified cereals, and failure to take a vitamin/mineral supplement. However, unlike vitamin $B_{12}$ levels, folate levels often increase rather than decline with age. High folic acid intake can occur if older adults regularly take a supplement and consume fortified cereals.[77,78]

Bleeding with resultant iron deficiency in older adults may be due to carcinoma, peptic ulcer, atrophic gastritis, drug-induced gastritis, postmenopausal vaginal bleeding, or bleeding hemorrhoids. Older women have a much lower incidence of IDA compared with younger, menstruating women. Until proven otherwise, iron deficiency in older adults should be considered a sign of chronic blood loss. Steps should be taken to rule out bleeding, especially from the GI or female reproductive tract. AI is more common in older adults, as diseases that contribute to AI such as cancer,

infection, and rheumatoid arthritis are more prevalent in this population.

### Laboratory Findings

For practical purposes, it is best to use usual adult reference values and WHO criteria for laboratory tests in older adults. Anemia in older adults usually is normocytic and mild, with Hb values ranging between 10 and 12 g/dL (100-120 g/L; 6.21-7.45 mmol/L) in most anemic patients.[68] Evaluation of an older patient should be similar to strategies described previously for younger adults, perhaps with more emphasis on identifying occult blood loss and vitamin $B_{12}$ deficiency. Vitamin $B_{12}$ deficiency may be present even when plasma levels of vitamin $B_{12}$ are within the normal range, but elevated MMA levels will reveal the deficiency. A refractory macrocytic anemia in older adults should raise suspicion of a myelodysplastic syndrome.

### Treatment

Treatment of anemia in older adults is the same as that described for each type of anemia previously discussed in this chapter. With IDA, it is essential to treat the underlying cause, if known (ie, bleeding), and administer iron supplementation. Lower doses of iron supplementation are often recommended in older adults (eg, 325 mg of ferrous sulfate once daily or every other day) to decrease the incidence of GI adverse effects, which can lead to additional morbidity and poor adherence. Vitamin $B_{12}$ can be repleted orally or parenterally. The dose for oral therapy is 1,000 to 2,000 µg daily depending on anemia severity and has been shown to be as effective as intramuscular injections. As with oral iron therapy, reticulocytosis often occurs within a week of Vitamin $B_{12}$ therapy. Folate deficiency is treated with folic acid supplementation at 1 mg daily. The goal of treatment of AI is resolution of the underlying cause, although curing the underlying chronic illness in older adults can be difficult. Routine treatment with ESAs is not standard of care for AI in older adults.

## ANEMIA IN PEDIATRIC POPULATIONS

### Epidemiology

Globally, anemia is a significant cause of morbidity and mortality in pediatrics with an incidence as high as 47% in pre-school aged children and the highest concentration of patients found in Africa and Southeast Asia.[79] In the United States, the WHO reported the incidence of anemia in the pediatric population as 6% in 2011.[80] IDA accounts for the most cases of anemia in children and the prevalence of iron deficiency is reported to be as high as 20% in low-income families, likely due to diet.[81] IDA is a leading cause of infant mortality around the world.[82] Data from NHANES III indicated that 9% of children ages 12 to 36 months in the United States had iron deficiency and 3% had IDA.[83,84] Lack of a normal Hb at birth directly affects nonstorage iron and increases the risk of IDA in the first 3 to 6 months of life. An anemia of prematurity most commonly occurs 3 to 12 weeks after birth in infants younger than 32 weeks gestation and can spontaneously resolve by 3 to 6 months. Additional causes of anemia in pediatrics include “physiologic anemia” in newborns, G6PD deficiency, and thalassemia.

### Etiology

The age of the child can yield some clues regarding the etiology of the anemia. From birth to 3 months, a “physiologic anemia” is the most common cause of anemia due to a decrease in erythropoiesis post-birth. At 3 to 6 months, hemoglobinopathy is more frequently encountered, as IDA is rare prior to 6 months of age. Iron deficiency becomes the most frequent etiology of anemia in toddler through adolescent years. The optimal amount of nutritional iron and folate required varies among individuals based on life-cycle stages. Two peak periods place children at risk of developing IDA. The first peak occurs during late infancy and early childhood, when children undergo rapid body growth, have low levels of dietary iron, and exhaust stores accumulated during gestation. The second peak occurs during adolescence, which is associated with rapid growth, poor diets, and onset of menses in girls. Some studies suggest that overweight children are at significantly higher risk for IDA. Proposed factors include genetic influences; physical inactivity, leading to decreased myoglobin breakdown and lower amounts of released iron into the blood; and inadequate diet with limited intake of iron-rich foods.[85]

Conditions in the newborn period that can lead to IDA include prematurity, low iron intake, and insufficient maternal iron consumption, particularly during the third trimester of pregnancy when 60% to 80% of fetal iron storage occurs. However, there is insufficient data to suggest that treatment of IDA in pregnant women will prevent IDA in newborns. Premature infants are at increased risk for IDA because of their smaller total blood volume,

increased blood loss through phlebotomy, and poor GI absorption. Factors leading to unbalanced iron metabolism in infants include insufficient iron intake, early introduction of cow's milk, intolerance of cow's milk, medications, and malabsorption. Dietary deficiency of iron in the first 6 to 12 months of life is less common today because of the increased use of iron supplementation during breast-feeding and use of iron-fortified formulas. Iron deficiency becomes more common when children change to regular diets.

When screening for iron deficiency in young children, a careful dietary history can help identify children at risk. High iron needs and the tendency to eat fewer iron-containing foods contribute to the etiology of iron deficiency during adolescence.

Other causes of microcytic anemia include thalassemia, lead poisoning, and sideroblastic anemia. Normocytic anemias in children include infection with human parvovirus B19 and glucose-6-phosphate dehydrogenase (G6PD) deficiency. In the setting of G6PD deficiency, a thorough review of potential drug and toxin exposure around the onset of anemia will be helpful to determine an offending agent. Macrocytic anemias are caused by deficiencies in vitamin $B_{12}$ and folate, chronic liver disease, hypothyroidism, and myelodysplastic disorders. Folic acid deficiency usually is due to inadequate dietary intake, but human milk and cow's milk provide adequate sources. Vitamin $B_{12}$ deficiency due to nutritional reasons is rare but may occur due to congenital pernicious anemia.

## Pathophysiology

In contrast to anemias in adults, which tend to be manifestations of a broader underlying pathology, anemias in the pediatric population are more often due to a primary hematologic abnormality. In newborn infants, "physiologic anemia" is often due to reduced EPO production.[86] Erythropoiesis also decreases during this time as a result of increased tissue oxygenation.

Hemoglobinopathy is often suspected in infants with anemia between the ages of 3 to 6 months because IDA is rare during this period. Potential causes include sickle cell anemia, thalassemia, and G6PD deficiency. Thalassemia is an inherited condition in which the Hgb structure is compromised leading to anemia of various degrees based on the subtype of thalassemia. This condition is most frequently seen in patients of Mediterranean and Southeast Asian heritage.[81] G6PD deficiency is an X-linked disorder most frequently seen in patients of Asian, Mediterranean, and African descent.[87] The lack of this enzyme reduces the RBC's protection against oxidative injury by limiting the glutathione available. Glutathione in RBCs rapidly inactivates oxidants preventing cellular injury. G6PD is an important enzyme in the formation of glutathione and a deficiency in this enzyme ultimately leads to hemolysis and anemia after exposure to an oxidant, such as dapsone, primaquine, or fava beans.

IDA should be suspected in microcytic anemia of children after 6 months of age. The amount of iron present at birth depends on gestational length and weight. Iron stores from birth are mostly depleted by 6 months of age. The addition of iron supplements and iron-enriched foods is important to maintain iron levels and prevent the development of IDA.

## Laboratory Findings

When evaluating laboratory values for pediatric patients, the clinician must use age- and sex-adjusted norms. It is important to know that many blood samples are capillary samples, such as heel or finger sticks, which may have slightly different results than venous samples. The USPSTF has concluded that evidence is insufficient to recommend for or against routine screening for IDA in asymptomatic low-risk children aged 6 to 12 months. Hb is a sensitive test for iron deficiency, but it has low specificity in childhood anemias. If an abnormality is found, a CBC should be ordered to evaluate MCV and determine whether the anemia is microcytic, normocytic, or macrocytic. A peripheral blood smear and reticulocyte count also may be helpful. The peripheral blood smear can indicate the etiology based on RBC morphology, and the reticulocyte count helps differentiate between decreased RBC production and increased RBC destruction or loss. Other laboratory tests include serum iron, ferritin, TIBC, and transferrin saturation. Laboratory markers of hemolysis, including increased bilirubin, lactate dehydrogenase, and decreased haptoglobin, can identify hemolytic anemias, including G6PD deficiency and thalassemia. A G6PD deficiency screening test may be indicated if hemolysis is present. Mild hereditary anemias may produce a mild hypochromic microcytic anemia that can be confused with IDAs. The RDW may be high with iron deficiency and is more likely to be normal with thalassemia. Laboratory features of anemia of prematurity include normocytic normochromic cells, low reticulocyte count, low serum EPO concentrations, and decreased RBC precursors in bone marrow. Laboratory diagnosis of vitamin $B_{12}$ and folate deficiency in children is similar to that of adults.

## Treatment

Primary prevention of IDA in infants, children, and adolescents is the most appropriate goal because delays in mental and motor development are potentially irreversible. In 2015, the USPSTF published revised recommendations to screen and supplement iron deficiency in the United States, focusing on children and pregnant women. They concluded that the current evidence is insufficient to evaluate the benefits and harms of routine screening in asymptomatic children ages 6 to 24 months and routine use of iron supplementation in pregnant women to improve fetal outcomes.[88] Screening should be restricted to high risk children, including those with poor growth and insufficient iron intake. Routine iron supplementation for exclusively breastfed infants at 1 mg/kg/day is recommended by the American Academy of Pediatrics (AAP) beginning at 4 months until appropriate iron-containing foods are introduced. Fair evidence was found that iron supplementation (eg, iron-fortified formula or iron supplements) improves neurodevelopmental outcomes in children at risk for IDA. Due to the widespread use of iron-enriched formula, additional supplementation is rarely necessary in formula-fed infants.[80]

Interventions likely to prevent anemia include diverse foods with bioavailable forms of iron, food fortification for infants and children, and individual supplementation. Routine screening for iron deficiency in nonpregnant adolescents is recommended only for those with risk factors, which include vegetarian diets, malnutrition, low body weight, chronic illness, or history of heavy menstrual blood loss.

For infants aged 9 to 12 months with a mild microcytic anemia, the most cost-effective treatment is a therapeutic trial of iron. $Fe^{2+}$ sulfate at a dose of 3 to 6 mg/kg/day of elemental iron divided once or twice daily between meals for 4 weeks is recommended. In children who respond, iron should be continued for 2 more months to replace storage iron pools, along with dietary intervention and patient education.[89] Liquid iron preparations can occasionally stain teeth. Kids should be advised to brush teeth or rinse out their mouth after administration. Parenteral iron therapy has a limited role and is rarely necessary.

For the macrocytic anemias in children, folate can be administered at a dose of 1 mg daily. However, vitamin $B_{12}$ deficiency due to congenital pernicious anemia requires lifelong vitamin $B_{12}$ supplementation. Dose and frequency should be titrated according to clinical response and laboratory values. No data regarding the use of oral vitamin $B_{12}$ supplementation in children is available.

Treatment of normocytic anemias is based on underlying cause.

## EVALUATION OF THERAPEUTIC OUTCOMES

For IDA, a positive response to a trial of oral iron therapy is characterized by modest reticulocytosis in days, with an increase in Hb starting after about 2 weeks with continued rapid rise in Hb. As the Hb level approaches normal, the rate of increase slows progressively. Hb should reach a normal level after about 2 months of therapy and often sooner.[12] If the patient does not develop reticulocytosis, reevaluation of the diagnosis or iron replacement therapy is necessary. Iron therapy should continue for a period sufficient for complete restoration of iron stores. Serum ferritin concentrations should return to the normal range prior to discontinuation of iron. The time interval required to accomplish this goal varies, although at least 6 to 12 months of therapy usually is warranted.

When large amounts of parenteral iron are administered, by either total dose infusion or multiple intramuscular or IV doses, the patient's iron status should be closely monitored. Patients receiving regular IV iron should be monitored for clinical or laboratory evidence of iron toxicity or overload. Iron overload may be indicated by abnormal hepatic function tests, serum ferritin greater than 800 ng/mL (800 µg/L [1,800 pmol/L]), or transferrin saturation greater than 50%. Serum ferritin and transferrin saturation should be measured in the first week after larger IV iron doses. Hb and Hct should be measured weekly, and serum iron and ferritin levels should be measured at least monthly.

Most patients with vitamin $B_{12}$–deficiency anemia respond rapidly to vitamin $B_{12}$ therapy. The typical patient will experience improved strength and well-being within a few days of treatment initiation. Reticulocytosis is evident in 3 to 5 days. Hb begins to rise after the first week and should normalize in 1 to 2 months.[90] CBC and serum cobalamin levels usually are drawn 1 to 2 months after initiation of therapy and 3 to 6 months thereafter for surveillance monitoring. Homocysteine and MMA levels can be repeated 2 to 3 months after initiation of replacement therapy to evaluate for normalization of levels, although levels begin to decrease in 1 to 2 weeks. Neuropsychiatric signs and symptoms can be reversible if treated early. If permanent neurologic damage has resulted, progression should cease with replacement therapy. Slow response to therapy or failure to observe normalization of laboratory results may suggest the presence of an additional abnormality such as iron deficiency, thalassemia trait, infection, malignancy, nonadherence, or misdiagnosis.

In folic acid deficiency anemia, symptomatic improvement, as evidenced by increased alertness and appetite, often occurs early during treatment. Reticulocytosis begins in the first week. Hct begins to rise within 2 weeks and should reach normal levels within 2 months. MCV initially increases because of an increase in reticulocytes but gradually decreases to normal.

One of the earliest responses with ESA use is an increased blood reticulocyte count, which usually occurs in the first few days. Baseline iron status should be checked before and during treatment, as many patients receiving ESAs require supplemental iron therapy. The optimal form and schedule of iron supplementation are not known. Hb levels should be monitored twice a week until stabilized. Hb should also be monitored twice weekly for 2 to 6 weeks after a dose adjustment.[54] A fall in Hb during ESA therapy may indicate a need for iron supplementation or signal occult blood loss. Baseline and periodic monitoring of iron, TIBC, transferrin saturation, or ferritin levels may be useful in optimizing iron repletion and limiting the need for ESAs. Patients who do not respond to 8 weeks of optimal dosage should not continue taking ESAs. Target Hb levels should be 11 to 12 g/dL (110-120 g/L; 6.83-7.45 mmol/L). Cost is an issue with ESA therapy. Therefore, drug cost must be weighed against the effects on transfusions and hospitalizations.

In older adults, responses and treatment monitoring are similar as that described for the general adult population. If the reticulocyte count rises but the anemia does not improve, inadequate absorption of iron or continued blood loss should be suspected. As with any form of anemia, symptomatic improvement should be evident shortly after starting therapy and Hb/Hct should begin to rise within a few weeks of initiating therapy. A key component of symptom assessment among older adults is the functional domain. Patients should be asked about changes in self-care abilities, mobility, and stamina.

Therapeutic outcomes are assessed in children by monitoring Hb, Hct, and RBC indices 4 to 8 weeks after initiation of iron therapy. For premature infants, Hb or Hct should be monitored weekly.

## CONCLUSION

Anemia affects many patients across the lifespan, impacting morbidity and mortality. The causes of anemia can vary and includes genetic disorders, nutritional deficiencies, chronic disease, and acute illness. Identification of the correct cause of anemia through lab assessment is key to selecting the appropriate treatment and monitoring plan. While anemia can sometimes be a symptom or complication of another disease or deficiency, it is important for clinicians to understand the disease and how to treat it.

## ABBREVIATIONS

| | |
|---|---|
| ACD | anemia of chronic disease |
| AI | anemia of inflammation |
| CBC | complete blood count |
| CDC | Centers for Disease Control and Prevention |
| EPO | erythropoietin |
| ESA | erythropoiesis-stimulating agent |
| $Fe^{2+}$ | ferrous iron |
| $Fe^{3+}$ | ferric iron |
| G6PD | glucose-6-phosphate dehydrogenase |
| Hb | hemoglobin |
| Hct | hematocrit |
| HIV | human immunodeficiency virus |
| IDA | iron-deficiency anemia |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| MMA | methylmalonic acid |
| NHANES | National Health and Nutrition Examination Survey |
| NSAID | nonsteroidal anti-inflammatory drugs |
| RBC | red blood cell |
| RDW | red blood cell distribution width |
| TIBC | total iron-binding capacity |
| USPSTF | United States Preventive Services Task Force |
| WHO | World Health Organization |

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## SELF-ASSESSMENT QUESTIONS

1. Classification of anemias is *not* based on:

   A. Pathophysiology

   B. Morphology

   C. RBC indices

   D. Etiology

2. Stimulation of erythropoiesis

   A. Is due to a decrease in tissue oxygen levels

   B. Results in decreased release of reticulocytes from the bone marrow

   C. Is due to an increase in tissue oxygen levels

   D. Is due to rising levels of erythropoietin from the liver

3. Serum iron levels in iron deficiency anemia:

   A. May remain within the normal range

   B. May have a 20% to 30% diurnal variation

   C. Reflect the concentration of iron bound to transferrin

   D. All of the above

4. Iron is *best* absorbed:

   A. From vegetables

   B. With concurrent tea administration

   C. In the ferrous form

   D. In an alkaline environment

5. Which one of the following is *correct* regarding therapeutic doses of oral iron?

   A. The enteric formulation results in increased iron absorption.

   B. Reticulocytosis occurs within 7 days after initiation of therapy.

   C. Iron therapy should be continued for 1 week of therapy and then discontinued.

   D. Oral iron should preferably be administered in a single dose with food.

6. Which of the following is an appropriate lab to help differentiate between vitamin $B_{12}$ deficiency and folate deficiency in an anemic patient?

   A. Homocysteine

   B. Hemoglobin

   C. MMA (methylmalonic acid)

   D. MCV (mean cell volume)

7. Parenteral iron therapy:

   A. Is best administered IV rather than IM

   B. Should be given initially as a loading dose

   C. Requires concurrent erythropoietin therapy

D. Should be given if Hgb does not increase within 7 days of oral iron therapy initiation

8. Which one of the following is *correct* regarding the treatment of vitamin $B_{12}$ deficiency?

   A. Neurological manifestations are reversible regardless of the length of vitamin $B_{12}$ deficiency.

   B. Vitamin $B_{12}$ tablets that are available over the counter can be used in many cases to treat deficiency.

   C. Vitamin $B_{12}$ given via nasal spray can be used when neurological symptoms are present.

   D. Oral replacement therapy cannot be utilized if a patient lacks intrinsic factor.

9. Which one of the following is *correct* regarding folic acid deficiency anemia?

   A. Folate is synthesized in the human body.

   B. Ingestion of alcohol interferes with the absorption of folate.

   C. Folic acid deficiency anemia results in neurologic manifestations.

   D. Supplementation with folic acid 1 µg daily will replenish folate stores.

   E. Serum concentrations of methylmalonic acid and homocysteine are elevated.

10. Patients with anemia of chronic disease

    A. Have decreased levels of iron in the bone marrow

    B. Can be clearly identified from a review of laboratory values

    C. May have a normal ferritin

    D. Respond best to oral iron therapy during inflammation

11. Which of the following statements is true regarding production/maturation of RBCs?

    A. The main site of production of RBCs is the spleen.

    B. As oxygen levels start to decrease, less erythropoietin is produced.

    C. A pluripotent stem cell always becomes a red blood cell.

    D. The bone marrow releases reticulocytes into the circulation.

12. Which one of the following statements is *incorrect* regarding adherence to anemia therapy?

    A. Patients may cease taking oral iron therapy due to concerns regarding the development of dark stools.

    B. Oral iron therapy may result in diarrhea or constipation.

    C. Patients may be nonadherent to parenteral routes of vitamin $B_{12}$ supplementation due to fear of injections.

    D. Combination of iron products containing stool softeners are beneficial to avoid constipation.

13. Which of the following medications could affect how well iron is absorbed?

    A. Warfarin

B. Methotrexate

C. Omeprazole

D. Metformin

14. Which of the following gives you the best estimation of total iron stores in the body?

A. Serum iron

B. Ferritin

C. Total iron binding capacity

D. Transferring saturation

15. Which of the following statements is TRUE regarding production/maturation of red blood cells?

A. The main site of production of red blood cells is the spleen.

B. A pluripotent stem cell always becomes a red blood cell.

C. The bone marrow releases reticulocytes in the circulation.

D. Erythropoietin acts mainly on the kidneys to produce red blood cells.

## SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Anemia classification can be done through various methods. However, red blood cell indices do not always distinguish between different types of anemias. For example, in vitamin $B_{12}$ deficiency and folic acid deficiency anemia, the MCV can be elevated. These indices can give clues about types of anemias, but are not definitive.

2. **A.** Erythropoiesis increases when there is a drop in tissue oxygen levels. When this happens, the kidney produces more erythropoietin that stimulates the bone marrow to release more reticulocytes.

3. **D.** Initially, serum iron levels may not drop below normal range, despite the patient having iron deficiency anemia, due to the iron stores in the body. There is variation in this level depending on the time of the day and this level also represents iron is bound to transferrin.

4. **C.** There are several things that decrease oral iron absorption. Heme iron is better absorbed and this type of iron comes more from meats and not vegetables. Tea and wine due to the tannins decrease absorption. An acidic environment in the stomach increases absorption. Medications that suppress acid and make it more alkaline decrease absorption.

5. **B.** The recommended oral dose can be around 60- to 65-mg elemental iron daily, some evidence may suggest a lower dose or this amount several times per week. Food decreases absorption of iron. Enteric formulations do not allow iron to be released in the stomach. Lastly, iron therapy should be continued for several months following labs and symptoms returning to normal.

6. **C.** MCV, homocysteine, and hemoglobin will be decreased in both folate deficiency and vitamin $B_{12}$ deficiency. Vitamin $B_{12}$ is required for an enzymatic reaction with MMA, a deficiency in $B_{12}$ results in increased levels. Folate is not involved in this reaction.

7. **A.** Intramuscular iron therapy results in adverse skin reactions and staining, the preferred route is IV. Loading doses are typically not used with parenteral iron and the rate at which it is given is important to avoid infusion reactions. Erythropoietin is not required for IV iron therapy and hemoglobin will likely take longer to rise than 1 week.

8. **B.** Vitamin $B_{12}$ replacement with 1,000 mg can be done with a nonprescription formulation found in almost all pharmacies. If neurological

symptoms are present, intramuscular is preferred prior to oral replacement. If neurological symptoms from $B_{12}$ deficiency are present for an extended period of time they can become irreversible. There is absorption of $B_{12}$ via passive diffusion that does not rely on intrinsic factor, which allows for oral replacement in those patients lacking it.

9. **B.** Heavy alcohol use decreases the absorption of folate. Supplementation is necessary with oral folic acid 1 mg daily, in most cases, as it is not synthesized by the body. A distinguishing feature of folate deficiency from $B_{12}$ is that in folate deficiency MMA is not elevated and there are no neurological complications from deficiency.

10. **C.** Ferritin is an acute-phase reactant during inflammation. This level may be elevated in some anemia of chronic disease patients due to the ongoing inflammation. Even though this level is elevated, the patient may still be functionally iron deficient. Iron can be sequestered in the bone marrow during anemia of chronic disease and unavailable for use. These factors can make evaluation of lab parameters difficult in some patients.

11. **D.** A pluripotent stem cell can differentiate into several different types of cells, like red blood cells or white blood cells. Red blood cell production occurs mainly in the bone marrow, while destruction happens in the spleen. When oxygen levels drop in a normal patient, the kidney produces more erythropoietin to help the bone marrow produce and release more reticulocytes.

12. **D.** Iron products can cause diarrhea or constipation in patients. Typically, if constipation is caused it does not respond as well to a stool softener and a stimulant laxative may be needed. A common adverse effect of oral iron therapy is dark, black stools. Fear of injections could limit one's ability to treat with parenteral vitamin $B_{12}$.

13. **C.** An acidic environment in the stomach helps iron to be best absorbed. Omeprazole can lower the acid in the stomach and can decrease iron absorption. Metformin affects vitamin $B_{12}$ absorption. Methotrexate can interfere with folic acid absorption. Warfarin does not affect absorption of any of the vitamins/minerals discussed in this chapter.

14. **B.** Serum iron, transferrin saturation, and total iron binding capacity do not measure actual stores in the body, they reflect how much iron is in the blood. Ferritin measures iron stores.

15. **C.** Bone marrow is the primary site of red blood cell production and young red blood cells, reticulocytes are released from there into the circulation to further mature. The spleen is the main site of red blood cell destruction. A pluripotent stem cell can become other types of cells, not just a red blood cell. Erythropoietin does act on the kidney but its action on the bone marrow stimulates production of red blood cells.