Chapter 33: Anemias

INTRODUCTION

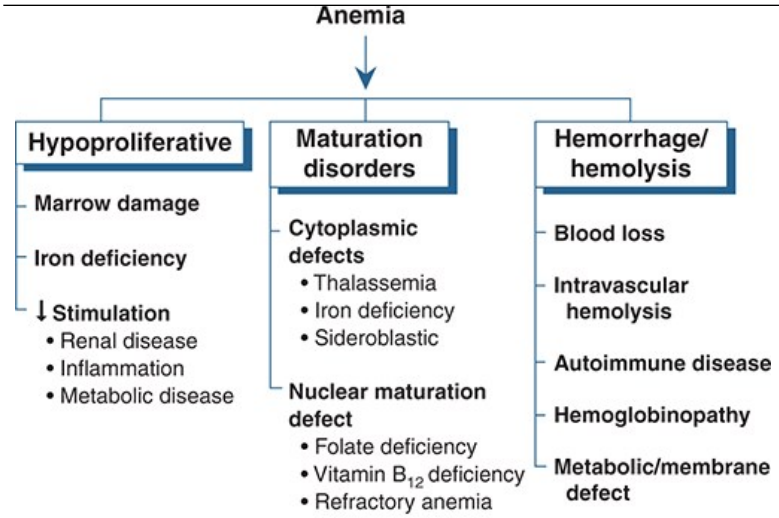
- *Anemia* is a group of diseases characterized by a decrease in either hemoglobin (Hb) or the volume of red blood cells (RBCs), resulting in decreased oxygen-carrying capacity of blood. The World Health Organization defines anemia as Hb less than 13 g/dL (130 g/L; 8.07 mmol/L) in men or less than 12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

PATHOPHYSIOLOGY

- The functional classification of anemias is found in **Fig. 33-1**. The most common anemias are included in this chapter.
- Morphologic classifications are based on cell size. Macrocytic cells are larger than normal and are associated with deficiencies of vitamin B_{12} or folic acid. Microcytic cells are smaller than normal and are associated with iron deficiency, whereas normocytic anemia may be associated with recent blood loss or chronic disease.
- Iron-deficiency anemia (IDA), characterized by decreased levels of ferritin (most sensitive marker) and serum iron, and decreased transferrin saturation, can be caused by inadequate dietary intake, inadequate gastrointestinal (GI) absorption, increased iron demand (eg, pregnancy), blood loss, and chronic diseases.
- Vitamin B_{12}– and folic acid–deficiency anemias, macrocytic in nature, can be caused by inadequate dietary intake, malabsorption syndromes, and inadequate utilization. Deficiency of intrinsic factor causes decreased absorption of vitamin B_{12} (ie, pernicious anemia). Folic acid–deficiency anemia can be caused by hyperutilization due to pregnancy, hemolytic anemia, myelofibrosis, malignancy, chronic inflammatory disorders, long-term dialysis, or growth spurt. Drugs can cause anemia by reducing absorption of folate (eg, phenytoin) or through folate antagonism (eg, methotrexate).
- Anemia of inflammation (AI) is a newer term used to describe both anemia of chronic disease and anemia of critical illness. A diagnosis of exclusion, AI is an anemia that traditionally has been associated with malignant, infectious, or inflammatory processes, tissue injury, and conditions associated with release of proinflammatory cytokines. Serum iron is decreased but in contrast to IDA, the serum ferritin concentration is normal or increased. See **Table 33-1** for diseases associated with AI. For information on anemia of chronic kidney disease, see Chapter 75.
- Age-related reductions in bone marrow reserve can render elderly patients more susceptible to anemia caused by multiple minor and often unrecognized diseases (eg, nutritional deficiencies) that negatively affect erythropoiesis.
- Pediatric anemias are often due to a primary hematologic abnormality. The risk of IDA is increased by rapid growth spurts and dietary deficiency.

FIGURE 33-1

Functional classification of anemia. Each of the major categories of anemia (hypoproliferative, maturation disorders, and hemorrhage/hemolysis) can be further subclassified according to the functional defect in the several components of normal erythropoiesis.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TABLE 33-1

Diseases Causing Anemia of Inflammation

Common causes
Chronic infections
Tuberculosis
Other chronic lung infections (eg, lung abscess, bronchiectasis)
Human immunodeficiency virus
Subacute bacterial endocarditis
Osteomyelitis
Chronic urinary tract infections
Chronic inflammation
Rheumatoid arthritis
Systemic lupus erythematosus
Inflammatory bowel disease
Inflammatory osteoarthritis
Gout
Other (collagen vascular) diseases
Chronic inflammatory liver diseases
Malignancies
Carcinoma
Lymphoma
Leukemia
Multiple myeloma
Less common causes
Alcoholic liver disease
Congestive heart failure
Thrombophlebitis
Chronic obstructive pulmonary disease
Ischemic heart disease

CLINICAL PRESENTATION

- Signs and symptoms depend on rate of development and age and cardiovascular status of the patient. Acute-onset anemia is characterized by cardiorespiratory symptoms such as palpitations, angina, orthostatic light-headedness, and breathlessness. Chronic anemia is characterized by weakness, fatigue, headache, orthopnea, dyspnea on exertion, vertigo, faintness, cold sensitivity, pallor, and loss of skin tone.
- IDA is characterized by glossal pain, smooth tongue, reduced salivary flow, pica (compulsive eating of nonfood items), and pagophagia (compulsive eating of ice).
- Neurologic effects (eg, numbness and paraesthesisas) of vitamin B_{12} deficiency may precede hematologic changes. Psychiatric findings, including irritability, depression, and memory impairment, may also occur with vitamin B_{12} deficiency. Anemia with folate deficiency is not associated with neurologic symptoms.

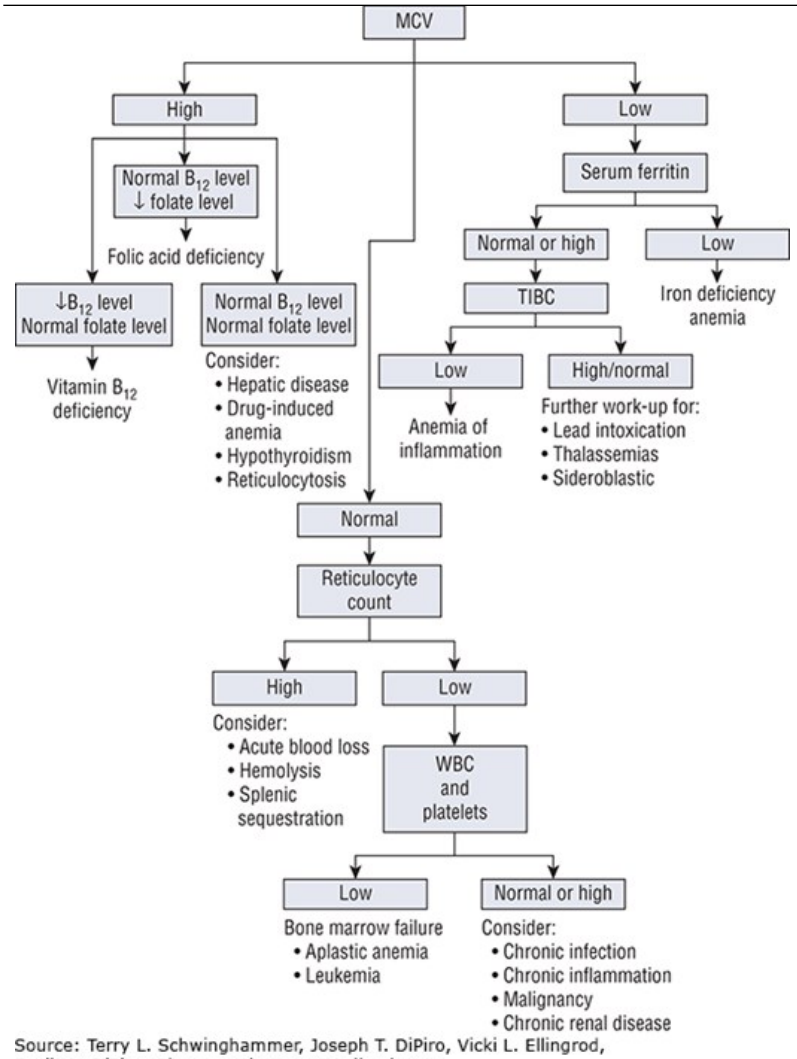
DIAGNOSIS

- Rapid diagnosis is essential because anemia is often a sign of underlying pathology. Severity of symptoms does not always correlate with the degree of anemia.
- Initial evaluation of anemia involves a complete blood cell count (CBC), reticulocyte index, and examination of the stool for occult blood. **Figure 33-2** shows a broad, general algorithm for the diagnosis of anemia based on laboratory data.
- The earliest and most sensitive laboratory change for IDA is decreased serum ferritin (storage iron), which should be interpreted in conjunction with decreased transferrin saturation and increased total iron-binding capacity (TIBC). Hb, hematocrit (Hct), and RBC indices usually remain normal until later stages of IDA.
- In macrocytic anemias, mean corpuscular volume is usually elevated to greater than 100 fL. Vitamin B_{12} and folate concentrations can be measured to differentiate between the two deficiency anemias. A vitamin B_{12} value less than 200 pg/mL (148 pmol/L), together with appropriate peripheral smear and clinical symptoms, is diagnostic of vitamin B_{12}–deficiency anemia. A decreased RBC folate concentration (less than 150 ng/mL [340 nmol/L]) appears to be a better indicator of folate-deficiency anemia than a decreased serum folate concentration (less than 3 ng/mL [7 nmol/L]).
- The diagnosis of AI is usually one of exclusion, with consideration of coexisting iron and folate deficiencies. Serum iron is usually decreased, but, unlike IDA, serum ferritin is normal or increased, and TIBC is decreased. The bone marrow reveals an abundance of iron; the peripheral smear reveals normocytic anemia.
- Elderly patients with symptoms of anemia should undergo a CBC with peripheral smear and reticulocyte count and other laboratory studies as needed to determine the etiology of anemia.
- The diagnosis of anemia in pediatric populations requires use of age- and sex-adjusted norms for laboratory values.

FIGURE 33-2

General algorithm for diagnosis of anemias.

(↓ decreased; MCV, mean corpuscular volume; TIBC, total iron-binding capacity; WBC, white blood cells.)



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TREATMENT

- Goals of Treatment: The goals are to return hematologic parameters to normal, restore normal function and quality of life, and prevent long-term complications.

Iron-Deficiency Anemia

- **Oral iron** therapy with soluble ferrous iron salts, which are not enteric coated and not slow or sustained release, is recommended at a daily dosage of 150–200 mg elemental iron in two or three divided doses (see **Table 33-2**).
- Iron is best absorbed from meat, fish, and poultry. Administer iron at least 1 hour before meals because food interferes with absorption, but administration with food may be needed to improve tolerability.
- Consider **parenteral iron** for patients with iron malabsorption, intolerance of oral iron therapy, or nonadherence. The following formula can be used to estimate the total dose of parenteral iron needed to correct anemia:

  Dose of iron (mg) = whole blood hemoglobin deficit (g/dL) × body weight (lb) or Dose of iron (mg) = whole blood hemoglobin deficit (g/L) × body weight (kg) × 0.22

- An additional quantity of iron to replenish stores should be added (about 600 mg for women and 1000 mg for men).
- **Iron dextran**, **sodium ferric gluconate**, **iron sucrose**, **ferumoxytol**, and **ferric carboxymaltose** are available parenteral iron preparations with similar efficacy but different molecular size, pharmacokinetics, bioavailability, and adverse effect profiles (see Table 75–2).

TABLE 33-2

Oral Iron Products

Iron Salt	Percent Elemental Iron	Common Formulations and Elemental Iron Provided
Ferrous sulfate	20	60–65 mg/324–325 mg tablet 60 mg/5 mL syrup 44 mg/5 mL elixir 15 mg/1 mL drops
Ferrous sulfate (exsiccated)	30	65 mg/200 mg tablet 50 mg/160 mg tablet
Ferrous gluconate	12	38 mg/325 mg tablet 28–29 mg/240–246 mg tablet
Ferrous fumarate	33	66 mg/200 mg tablet 106 mg/324–325 mg tablet

Vitamin B_{12}–Deficiency Anemia

- Oral vitamin B_{12} supplementation is as effective as parenteral, even in patients with pernicious anemia, because the alternate vitamin B_{12} absorption pathway is independent of intrinsic factor. Initiate oral **cobalamin** at 1–2 mg daily for 1–2 weeks, followed by 1 mg daily.
- Parenteral therapy acts more rapidly than oral therapy and is recommended if neurologic symptoms are present. A popular regimen is IM **cyanocobalamin**, 1000 mcg daily for 1 week, then weekly for 1 month, and then monthly for maintenance therapy. Initiate daily oral cobalamin administration after symptoms resolve.
- Continue vitamin B_{12} for life in patients with pernicious anemia.

Folate-Deficiency Anemia

- Oral **folic acid**, 1 mg daily for 4 months, is usually sufficient for treatment of folic acid–deficiency anemia, unless the etiology cannot be corrected. If malabsorption is present, a dose of 1–5 mg daily may be necessary. Parenteral folic acid is available but rarely necessary.

Anemia of Inflammation

- Treatment of AI is less specific than that of other anemias and should focus on correcting reversible causes. Reserve iron therapy for an established IDA; iron is not effective when inflammation is present. RBC transfusions are effective but should be limited to episodes of inadequate oxygen transport and Hb of 7–8 g/dL (70–80 g/L; 4.34–4.97 mmol/L).
- **Erythropoiesis-stimulating agents (ESAs)** can be considered, but response can be impaired in patients with AI. The initial dosage for **epoetin alfa** is 50–100 units/kg three times weekly and **darbepoetin alfa** 0.45 mcg/kg once weekly. Iron, cobalamin, and folic acid supplementation may improve response to ESA treatment.

- Potential toxicities of exogenous ESA administration include increases in blood pressure, nausea, headache, fever, bone pain, and fatigue. Hb must be monitored during ESA therapy. An increase in Hb greater than 12 g/dL (120 g/L; 7.45 mmol/L) with treatment or a rise of greater than 1 g/dL (10 g/L; 0.62 mmol/L) every 2 weeks has been associated with increased mortality and cardiovascular events.
- In patients with anemia of critical illness, parenteral iron is often used but is associated with a theoretical risk of infection.

Anemia in Pediatric Populations

- Infants aged 9–12 months: Administer ferrous sulfate 3–6 mg/kg/day (elemental iron) divided once or twice daily between meals for 4 weeks. Continue for two additional months in responders to replace storage iron pools. The dose and schedule of vitamin B_{12} should be titrated according to clinical and laboratory response. The daily dose of folic acid is 1 mg.

EVALUATION OF THERAPEUTIC OUTCOMES

- IDA: Positive response to oral iron therapy is characterized by modest reticulocytosis in a few days with an increase in Hb seen at 2 weeks. Reevaluate the patient if reticulocytosis does not occur. Hb should return to normal after 2 months; continue iron therapy until iron stores are replenished and serum ferritin normalized (up to 12 months).
- Megaloblastic anemia: Signs and symptoms usually improve within a few days after starting vitamin B_{12} or folic acid therapy. Neurologic symptoms can take longer to improve or can be irreversible, but should not progress during therapy. Reticulocytosis should occur within 3–5 days. Hb begins to rise a week after starting vitamin B_{12} therapy and should normalize in 1–2 months. Hct should rise within 2 weeks after starting folic acid therapy and should normalize within 2 months.
- ESAs: Reticulocytosis should occur within a few days. Monitor iron, TIBC, transferrin saturation, and ferritin levels at baseline and periodically during therapy. The optimal form and schedule of iron supplementation are unknown. Discontinue ESAs if a clinical response does not occur after 8 weeks.
- Pediatrics: Monitor Hb, Hct, and RBC indices 4–8 weeks after initiation of iron therapy. Monitor Hb or Hct weekly in premature infants.

See Chapter 100, Anemias, authored by Kristen Cook and Devon M. Greer, for a more detailed discussion of this topic.