Pharmacotherapy 2

Anemia

Dr Enaam M. Al Momany
Faculty of Pharmaceutical Sciences
Department of Clinical Pharmacy and Pharmacy Practice

Anemia

General Principles

- ✓ Anemia is defined as a decrease in circulating RBC mass; the usual criteria in adults being Hgb < 12 g/ dL or Hct < 36% for nonpregnant women and Hgb < 13 g/ dL or Hct < 39% in men.

- ✓ Classification Anemia can be broadly classified into three etiologic groups:
  - blood loss (acute or chronic)
  - decreased RBC production
  - increased RBC destruction (hemolysis).

- ✓ Anemia can also be categorized by RBC size as microcytic, normocytic, or macrocytic.

Diagnosis

Anemia is always caused by an underlying disorder; thus, a careful evaluation to determine the etiology is required in each case.

❖ Clinical Presentation

✓ Acute anemia: Patients with abrupt onset of anemia tolerate diminished RBC mass poorly. Patients may have symptoms of fatigue, malaise, dyspnea, syncope/ presyncope, or angina.

✓ Chronic anemia: In contrast to acute anemia, patients with chronic anemia are less symptomatic, at times only presenting with fatigue or dyspnea with increased activity or exertion. However, patients usually have symptoms when Hgb < 7 g/ dL.

❖ Physical Examination

✓ Common signs and symptoms of anemia include pallor , tachycardia, hypotension, dizziness, tinnitus, headaches, decreased cognitive ability, fatigue, and weakness.

✓ Patients may also experience reduced exercise tolerance, dyspnea on exertion, and heart failure.

✓ High-output heart failure and hypovolemic shock may be seen in acute, severe cases.

❖ Diagnostic Testing

✓ Laboratories

- CBC, reticulocyte count, and inspection of the peripheral smear will guide further laboratory testing because they provide a morphologic classification and assessment of RBC production.

- The most useful red cell indices are:
  - ➢ Mean cellular volume (MCV): Measures the mean volume of the RBCs (80-96 fL)
  - ➢ Red cell distribution width (RDW): Reflects the variability in the volume of the RBCs

- The relative reticulocyte count measures the percentage of immature red cells in the blood and reflects production of RBCs in the bone marrow.

✓ Diagnostic Procedures

- A BM biopsy is often indicated in cases of unexplained anemia with a low reticulocyte count or with anemia associated with other cytopenias.

Anemias Associated With Decreased Red Blood Cell Production

Iron Deficiency Anemia (IDA)

General Principles

- ✓ Iron deficiency is the most common cause of anemia in the ambulatory setting and is usually a chronic microcytic anemia with a low reticulocyte count.

- ✓ The most common causes of IDA are blood loss (e.g., menses, GI blood loss), decreased absorption (e.g., achlorhydria, celiac disease, bariatric surgery, H. pylori infection), and increased iron requirement (e.g., pregnancy).

Diagnosis

✓ Clinical Presentation

- Patients often present with cold intolerance along with fatigue or malaise that is typically worsened with activity.

- Pica (consumption of substances of no nutritional value as starch, or clay) occurs in about 25% of patients with chronic IDA and rarely occurs in other clinical settings.

- Pallor is a common physical finding in patients with IDA but is not specific.

✓ Diagnostic Testing

- Peripheral blood smear may show hypochromia (increased central pallor of RBCs), microcytosis, and pencil-shaped cells.

- The reticulocyte count is inappropriately low in IDA.

✓ Laboratories

- Ferritin is the primary storage form for iron in the liver and is a specific marker of an absolute iron deficiency. The reference range is 30– 400 ng/ mL.

- A ferritin level of < 10 ng/ mL in women or < 20 ng/ mL in men almost always reflects low iron stores.

- Ferritin is an acute-phase reactant, so normal levels may be seen in inflammatory states despite low iron stores.

Treatment

✓ Oral iron therapy

- Given in stable patients with mild symptoms.
- Several different preparations are available (Table).
- Iron is best absorbed on an empty stomach.
- Oral iron ingestion may induce a number of GI side effects, including epigastric distress, bloating, and constipation. As a result, nonadherence is a common problem.
- These side effects can be decreased by initially administering the drug with meals or every other day and increasing the dosage as indicated/ tolerated.

- Ferrous sulfate is the most commonly prescribed formulation.
- If there are unacceptable side effects, consider using a lower dose or an alternative formulation such as ferrous gluconate or ferrous fumarate, which contain lower amounts of elemental iron and may be better tolerated.
- In general, patients responding to oral iron therapy should see an increase in reticulocyte count within 1 week of therapy; an increase in Hgb of 2 g/ dL every 3 weeks is expected.
- Treatment should be continued until the total iron deficit is replete.

TABLE 118-1 Oral Iron Products

Iron Salt	Percent Elemental Iron	Common Formulations and Elemental Iron Provided
Ferrous sulfate	20	60-65 mg/324-325 mg tablet 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

TABLE 118-2 Iron Salt–Drug Interactions

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

✓ Parenteral iron therapy

- There are several formulations of IV iron (Table).

- Indications for parenteral iron over oral iron include:
  - Poor absorption (e.g., inflammatory bowel disease, malabsorption)
  - Very high iron requirements that cannot be met with oral supplementation (e.g., ongoing bleeding)
  - Intolerance to oral preparations
  - Functional iron deficiency in chronic kidney disease (CKD)

- IV iron infusion should not be given in patients with an active infection (i.e., fever) owing to concern for increased adverse reactions.

- **Iron dextran** (INFeD) is a less-expensive agent and allows for high-dose repletion in a single dose; however, infusion can be complicated by serious side effects including anaphylaxis.

  - An IV test dose of 0.5 mL should be administered over 5-10 minutes at 30-60 minutes before the full dose.
  - Methylprednisolone, diphenhydramine, and 1: 1000 epinephrine 1-mg ampule (for SC administration) should be immediately available at all times during the infusion.
  - Delayed reactions to IV iron as arthralgia, myalgia, fever, pruritus & lymphadenopathy, may be seen within several days of therapy & usually resolve spontaneously or with NSAIDs.

- **Second-generation iron products** include ferric gluconate (Ferrlecit) and iron sucrose (Venofer) and can be given at a faster infusion rate than INFeD.

  - Anaphylaxis is rare, and a test dose is not needed; however, a single infusion is typically insufficient to replenish the entire iron deficit, so multiple doses are required.

- **Third-generation iron products** include ferumoxytol (Feraheme) and ferric carboxymaltose (Injectafer) and allow for administration of a high dose with a rapid infusion.

  - A rare complication is severe hypotension, which can be related to the rapidity of the injection.
  - Of note, ferumoxytol is also available as an MRI contrast agent and will transiently show a significant increase in iron stores in the liver.

IV Iron Preparations

Preparation	IV Administration	Caution
Iron dextran (INFeD)	The entire dose may be diluted and infused in one setting; 1000 mg can be given over 1 h.	A 0.5-mL test dose should be given; observe patient for at least 1 h before full dose.
Iron sucrose (Venofer)	Administered undiluted as slow IV injection or infusion in diluted solution: Injection: 100 mg over 2–5 min 200 mg over 2–5 min Infusion: 100 mg/100 mL over 15 min 300 mg/250 mL over 1.5 h 400 mg/250 mL over 2.5 h >500 mg/250 mL over 3.5 h	
Ferric gluconate (Ferrlecit)	Injection: 125 mg over 10 min Infusion: 125 mg/100 mL over 1 h	
Ferumoxytol (Feraheme)	510 mg over 20 min; given as 2 doses 7 d apart	Observe patient for at least 30 min after administration. Serious hypersensitivity reactions have been observed with rapid IV injection (<1 min).
Ferric carboxymaltose	750 mg over 15–30 min; given as 2 doses 7 d apart	

Macrocytic/ Megaloblastic Anemia

General Principles

- ✓ Megaloblastic anemia is a term used to describe disorders of impaired DNA synthesis in hematopoietic cells.
- ✓ Etiology: Vitamin B12 deficiency occurs insidiously over several years because daily vitamin B12 requirements are low compared to total body stores.
- ✓ Most cases of megaloblastic anemia are due to vitamin B12 deficiency.
- ✓ Vitamin B12 deficiency occurs in up to 20% of untreated patients within 8 years of partial gastrectomy and in almost all patients with total gastrectomy or pernicious anemia (PA).
- ✓ In nonvegan adults, vitamin B12 deficiency is almost always due to malabsorption.

- ✓ PA usually occurs in individuals > 40 years (mean age of onset, 60 years). Up to 30% of patients have a positive family history.
- ✓ PA is an immune-mediated disorder associated with other autoimmune disorders.
- ✓ In patients with PA, 90% have antiparietal cell antibodies, and 60% have anti-intrinsic factor antibodies.
- ✓ Other etiologies of vitamin B12 deficiency include pancreatic insufficiency, bacterial overgrowth, and intestinal parasites (Diphyllobothrium latum).
- ✓ Folate deficiency results from a negative folate balance arising from malnutrition, malabsorption, or increased requirement (pregnancy, hemolytic anemia).
- ✓ Patients on weight-losing diets, alcoholics, the elderly, and psychiatric patients are particularly at risk for nutritional folate deficiency.

✓ Folate deficiency may be seen in several settings:

- Pregnancy & lactation in which there is a three- to fourfold increased daily folate requirements.
- Folate malabsorption secondary to celiac disease or bariatric surgery.
- Drugs that can interfere with folate absorption include ethanol, trimethoprim, pyrimethamine, barbiturates, and sulfasalazine.
- Dialysis-dependent patients require more folate intake because of increased folate losses.
- Patients with hemolytic anemia, as sickle cell anemia, require increased folate for accelerated erythropoiesis.

Diagnosis

✓ Clinical Presentation:

- In addition to symptoms of anemia, vitamin B12 deficiency may demonstrate neurologic symptoms, such as peripheral neuropathy, paresthesias, lethargy, hypotonia, and seizures.

- Important physical findings include signs of poor nutrition, pigmentation of skin creases and nail beds, or glossitis.

- Neurologic complications may occur in the absence of anemia and may not fully resolve despite adequate treatment.

- Folic acid deficiency does not result in neurologic disease.

✓ Diagnostic Testing:

- Laboratories:

  - Macrocytic anemia is usually present unless there is also a coincident cause of microcytic anemia, and leukopenia and thrombocytopenia may occur.

  - The peripheral smear may show macro-ovalocytes; hypersegmented neutrophils (containing six or more nuclear lobes) are common.

  - LDH and indirect bilirubin are typically elevated, reflecting ineffective erythropoiesis and premature destruction of RBCs.

  - Serum vitamin B12 and folate levels should be measured.

- Serum methylmalonic acid (MMA) and homocysteine (HC) may be useful when the vitamin B12 is 100-400 pg/ mL (or borderline low as defined by the laboratory reference range).

- MMA and HC are elevated in vitamin B12 deficiency; only HC is elevated in folate deficiency.

- Detecting antibodies to intrinsic factor is specific for the diagnosis of PA.

Treatment

- ✓ Potassium supplementation may be necessary when treatment is initiated to avoid potentially serious arrhythmias due to transient hypokalemia induced by enhanced hematopoiesis.
- ✓ Reticulocytosis should begin within 1 week of therapy, followed by a rising of Hgb over 6– 8 weeks.
- ✓ Coexisting iron deficiency is present in one-third of patients and is a common cause for an incomplete response to therapy.
- ✓ Folic acid 1 mg PO daily is given until the deficiency is corrected. High doses of folic acid (5 mg daily) may be needed in patients with malabsorption syndromes.
- ✓ Vitamin B12 deficiency is corrected by administering cyanocobalamin. Initial treatment (1 mg/ d intramuscular cyanocobalamin) is typically administered in the setting of severe anemia, neurologic dysfunction, or chronic malabsorption. After 1 week of daily therapy, a commonly employed regimen is 1 mg/ wk given for 4 weeks and then 1 mg/ mo for life.

Anemia of Chronic Renal Insufficiency

General Principles

- ✓ It is attributed primarily to decreased endogenous erythropoietin (EPO) production and may occur as the creatinine clearance declines to below 50 mL/ min.

- ✓ Other causes including a functional iron deficiency may contribute to the etiology

Diagnosis

- ✓ RBCs are often normocytic and hypochromic.

- ✓ If the patient's creatinine level is > 1.8 mg/ dL, the primary cause of the anemia can be assumed to be EPO deficiency and/ or iron deficiency.

- ✓ Iron status should be evaluated in patients who are undergoing dialysis by obtaining levels of ferritin and transferrin saturation.

- ✓ Oral iron supplementation is not considered effective in CKD; therefore, parenteral iron is recommended.

Treatment

- ✓ Treatment has been revolutionized by erythropoiesis-stimulating agents (ESAs) including EPO and darbepoetin alfa.

- ✓ Therapy is initiated in predialysis patients who are symptomatic.

- ✓ Objective benefits of reversing anemia include enhanced exercise capacity, improved cognitive function, elimination of RBC transfusions, and reduction of iron overload.

- ✓ Subjective benefits include increased energy, enhanced appetite, better sleep patterns, and improved sexual activity.

- ✓ Administration of ESAs can be IV (hemodialysis patients) or SC (predialysis or peritoneal dialysis patients).

- ✓ In dialysis and predialysis patients with CKD, the target Hgb should be between 11– 12 g/ dL and should not exceed 12 g/ dL.

- ✓ Hgb and Hct should be measured at least monthly while receiving an ESA. Dose adjustments should be made to maintain the target Hgb.

- ✓ Side effects of ESAs:
  - Targeting higher Hgb levels and/ or exposure to high doses of ESAs is associated with a greater risk of CV complications and mortality.

  - In addition, a higher Hct level from ESAs increases the risk of stroke, HF, HTN & DVT.

- ✓ Suboptimal responses to ESA therapy are most often due to iron deficiency, inflammation, bleeding, infection, malignancy, malnutrition, and aluminum toxicity.

- ✓ Because anemia is a powerful determinant of life expectancy in patients on chronic dialysis, IV iron administration has become first-line therapy for individuals with transferrin saturation < 20% and/ or ferritin < 500 ng/ mL. It has also been shown to reduce the ESA dosage required to correct anemia.

- ✓ A ferritin level and transferrin saturation should be tested at least monthly during the initiation of ESA therapy with a goal ferritin level of > 200 ng/ mL and a transferrin saturation of > 20% in dialysis-dependent patients and a ferritin level of > 100 ng/ mL and a transferrin saturation of > 20% in predialysis or peritoneal dialysis patients.

- ✓ Iron therapy is unlikely to be useful if the ferritin level is > 500 ng/ mL.

Anemia of Chronic Disease

General Principles

- ✓ Anemia of chronic disease (ACD) often develops in patients with long-standing inflammatory diseases, malignancy, autoimmune disorders, and chronic infection.
- ✓ Etiology is multifactorial, including defective iron mobilization during erythropoiesis, inflammatory cytokine-mediated suppression of erythropoiesis, and impaired EPO response to anemia.
- ✓ Hepcidin is a critical regulator of iron homeostasis and is normally low when iron is deficient, allowing for increased iron absorption and utilization.
- ✓ Chronic inflammation increases hepcidin levels and causes a functional iron deficiency due to impaired iron recycling and utilization.
- ✓ Hepcidin is renally cleared, suggesting a role in anemia of chronic renal disease.

Diagnosis

- ✓ Anemia is normocytic in 75% of cases and microcytic in the remainder of cases.
- ✓ The soluble transferrin receptor level is helpful in differentiating ACD (normal) and iron deficiency (elevated) when the ferritin is indeterminate.
- ✓ Iron studies may show low serum iron and TIBC. Ferritin level below 30 ng/ mL suggests coexisting iron deficiency and should be treated with supplemental iron.

Treatment

- ✓ Therapy for ACD is directed toward the underlying disease and eliminating exacerbating factors such as nutritional deficiencies and marrow-suppressive drugs.
- ✓ Enteral iron is typically ineffective in ACD because of reduced intestinal absorption of iron.

- ✓ ESA therapy should be considered if the patient is transfusion dependent or has symptomatic anemia.
- ✓ ESA therapy is discontinued when the Hgb is > 11 g/ dL to reduce risk of CV adverse events.
- ✓ Suboptimal (< 1 g/ dL) increase in Hgb 2 weeks after ESA dose prompts a re-evaluation of iron stores.
- ✓ Effective doses of ESA are higher than those reported in anemia from renal insufficiency.
- ✓ If no responses have been observed at 900 units/ kg/ wk, further dose escalation is unlikely to be effective.

Drug-Induced Hemolytic Anemia

General Principles

- ✓ It is anemia resulting from exposure to a medication. Table 21-5 lists common offending medications.
- ✓ The most commonly implicated agents are cephalosporins, penicillins, NSAIDs, and quinine or quinidines.

Treatment

- ✓ If drug-induced hemolytic anemia is suspected, the most important treatment is discontinuation of the offending agent.

TABLE 21-5

Commonly Used Drugs That Can Induce Red Blood Cell Disorders

Sideroblastic Anemia	Aplastic Anemia[a]	G6PD Deficiency	Immune Hemolytic Anemia
Chloramphenicol	Acetazolamide	Dapsone	Cephalosporins (cefotetan, ceftriaxone)
Cycloserine	Antineoplastic drugs	Doxorubicin	Penicillins (piperacillin)
Ethanol	Carbamazepine	Methylene blue	Purine nucleoside analogues (fludarabine, cladribine)
Isoniazid	Chloramphenicol	Nalidixic acid	NSAIDs (diclofenac, ibuprofen)
Pyrazinamide	Gold salts	Nitrofurantoin	Quinidine
	Hydantoins	Pegloticase	Quinine
	Penicillamine	Phenazopyridine	Rifampin
	Sulfonamides	Primaquine	Sulfonamides (trimethoprim/sulfamethoxazole)
	Phenylbutazone	Rasburicase	
	Quinacrine	Sulfacetamide	
		Sulfamethoxazole	
		Sulfanilamide	
		Sulfapyridine	

Data compiled from multiple sources. Agents listed are available in the United States.

a Drugs with ≥30 cases reported; many other drugs rarely are associated with aplastic anemia and are considered low risk.

G6PD, glucose-6-phosphate dehydrogenase.