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Recommended Citation

Kucera A, Smith B, Tsu LV. Anemia and the Role of the Pharmacist. Arizona Journal of Pharmacy 2014; 31-35

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Anemia and the Role of the Pharmacist

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Goal:

This home-study CPE has been developed to educate pharmacists and pharmacy technicians about the various types of anemia and their treatments.

Objectives:

At the conclusion of this lesson, successful participants should be able to:

1. Identify signs and symptoms of anemia

2. Differentiate between types of anemia and their etiology

3. Perform patient counseling for oral iron therapy, including dosing, drug interactions and side effects

4. List goals of iron therapy

5. Name food sources rich in iron, folic acid and/or vitamin B12

6. Describe treatment of folic acid and vitamin B12 deficiency anemias

Introduction

Anemia, a condition characterized by decreased hemoglobin levels and an insufficient ability to oxygenate the body, is one of the most common blood disorders in the world. Globally, it affects over 1.6 billion people; roughly 25% of the world population.¹

In healthy individuals, oxygen is adequately transported throughout the body via hemoglobin (Hgb), a protein found in red blood cells (RBCs). RBCs require several nutrients to function properly including iron, folate and vitamin B12. A deficiency in any of these nutrients, alteration of morphology of the cell, increased RBC destruction or excessive blood loss can result in anemia.²

There are numerous causes of anemia including malnutrition, chronic conditions, pregnancy and drug-induced anemia.³ Additional risk factors for anemia include folic acid deficiency, vitamin B12 and autoimmune disorders ^(Table 1.1).

Healthy patients with anemia may be asymptomatic if their hemoglobin levels decrease slowly over time. Presentation with acute anemia may present as tachycardia or hypotension, while chronic conditions often present with more generalized symptoms like fatigue, weakness or pale skin ^{(Table 1.2).4,5}

Diagnosis

Although diagnosing anemia may be relatively straight forward, a thorough workup is generally required to identify the etiology of the disorder. Since there are many different causes of anemia it is important to identify the origin of the disorder so that it may be treated correctly and can be prevented in the future. Usually the assessment begins with a detailed history of the patient, including information such as diet and lifestyle, medical history, family history, current medications and religious practices that may influence their diet.⁶ Next, a physical exam is performed and several laboratory tests are completed.⁶ Laboratory tests commonly used for the diagnosis of anemia include a complete blood count (CBC), iron studies, and serum nutrient levels.^{6,7,8} Table 1.3 contains common laboratory tests used to diagnose anemia and explains what each test assesses. There are three broad categories of anemia which are differentiated by their mean cell volume (MCV) which measures the size of the RBCs. As depicted in Table 1.3. normal values for MCV range from 80-100 fL/ cell.⁹ Macrocytic anemias, also known as megaloblastic anemias, have a MCV level greater than these values. and include folic acid deficiency anemia. vitamin B12 deficiency anemia and pernicious anemia.¹⁰ Microcytic anemias have decreased MCV values and include iron deficiency anemia. Finally, normocytic anemias have MCV values that are within normal limits, and the RBCs present in these patients are generally unaffected. These anemias are caused by acute blood loss or abnormal blood cell production, such as aplastic anemia or anemia from chronic renal disease.^{4,11,12} Assessment of a MCV value provides a general classification of the anemia and gives the provider a better idea of what potential causes may be.

Microcytic Anemias

Iron Deficiency Anemia:

Iron deficiency anemia, a microcytic anemia⁶, is the most common type of anemia in the world.³ As indicated by its name, iron deficiency anemia is the result of insufficient iron in the blood. There are various causes of iron deficiency, such as insufficient consumption in the diet, malabsorption, heavy menstruation, pregnancy, dialysis and gastrointestinal inflammatory disorders.^{3,6} On presentation, this type of anemia may differentiate from others with specific signs and symptoms. These signs include tongue soreness or smooth appearance, pica, phagophagia, and/or dry mouth.⁴ Table 2.1 contains symptoms of specific anemias. Suspicion of iron deficiency anemia is verified via analysis of iron indices and of other labs included in Table 1.3. Patients with iron deficiency anemia will have decreased serum iron, ferritin and transferrin saturation (TSAT) levels and an

Anemia

increased total iron-binding capacity (TIBC).⁷ Additionally, patients with anemia will frequently show hemoglobin levels below 13 g/dL in men and 12 g/dL in women.¹

Once a specific diagnosis of iron deficiency anemia has been determined, there are several methods of treatment that can be attempted. Generally, mild iron deficiency can be treated on an outpatient basis with oral iron replacement therapy, with a goal of 200 mg of elemental iron per day. There are currently four oral iron supplements available on the market commonly used for treatment: ferrous gluconate, ferrous sulfate, ferrous fumarate, and polysaccharide iron complex. Table 2.2 describes these oral iron products and their elemental iron content. Of these four, ferrous sulfate is prescribed most commonly and is likely the oral therapy encountered most often in community pharmacies.³

To ensure that patients get maximum benefit out of oral iron therapy, medication counseling should be performed. Regimens of iron supplements should be divided into two to three doses daily. These supplements should be taken on an empty stomach, an hour before meals or two hours following a meal. Oral iron has been found to have increased absorption when taken with ascorbic acid, so it is often recommended that these supplements be taken with a glass of orange juice.³

Side effects of oral iron therapy are mostly inflicted on the gastrointestinal (GI) tract, and include abdominal pain, nausea, constipation, heartburn and dark stools. It is because of this GI upset that one-time daily dosing should be avoided.^{13,14,15,16} If the patient experiences GI side effects that are intolerable, it is recommended that the supplements be taken with orange juice and/or food. There are several drug-drug interactions of oral iron supplements that the pharmacist should be cautious of when filling a prescription. Table 2.3 lists these interactions.

To assess response to oral iron therapy labs will need to be monitored. Reticulocyte count, an assessment of the production of new RBCs, should increase within seven to ten days. Hemoglobin (Hgb) and hematocrit (Hct) should also be tracked with an expected increase in Hgb of 1g/dL per week and at least 2g/dL total by three weeks of therapy.⁶

Educating patients about dietary sources of iron is an important intervention for both treatment of deficiency and for preventing future occurrence of anemia. Meat is a good source of iron, including red meat, chicken, fish and organ meats (i.e. liver). Other sources include beans, green leafy vegetables and enriched breakfast cereals. These non-meat sources contain "non-heme" iron, which have a lower rate of absorption than "heme" iron found in meat. Therefore, it is often difficult for vegetarians to achieve recommended levels of intake of iron. In this patient population, iron-containing dietary supplements may be considered for prophylaxis.17

In severe cases of iron deficiency anemia, if the patient is unable to tolerate oral therapy or if there is an inadequate response to oral therapy, parenteral iron therapy is indicated.³ There are currently four parenteral iron products commonly used: iron dextran, iron sucrose and sodium ferric gluconate and ferric carboxymaltose. Table 2.4 describes these products and their recommended doses.

All parenteral iron products have a risk of anaphylaxis, with the highest risk associated with iron dextran. Due to this high risk, a test dose is required prior to administering iron dextran.¹⁸ Other adverse effects of intravenous iron include arrhythmias, arthralgia, hypotension, flushing and prurtitis.^{18,19,20,21} Two formulations, iron sucrose and sodium ferric gluconate, are only FDA approved for the treatment of anemia associated with chronic kidney disease (CKD).^{19,20}

Macrocytic Anemias

Vitamin B12 Deficiency and Pernicious Anemias:

Vitamin B12 deficiency anemia, a macrocytic anemia, is one of the most common types of anemia in the United States.²² A deficiency of vitamin B12 can be caused by several factors, including diet, malabsorption, alcoholism, or decreased stomach acidity.²³ Certain medications can also lead to deficiency such as proton pump inhibitors and metformin. A severe form of vitamin B12 deficiency is called pernicious anemia. Pernicious anemia is a specific type of anemia that is caused by autoimmune destruction of gastric parietal cells. In healthy individuals these cells produce intrinsic factor (IF) which is required to bind and absorb dietary vitamin B12. When autoimmune destruction of the gastric parietal cells takes place, vitamin B12 can no longer be absorbed and deficiency occurs.²⁴

Specific signs and symptoms differentiate these two types of anemia from others such as numbness, parasthesias and gait disturbances.²³ See Table 2.1 for additional symptoms. Development and myelination of the central nervous system requires vitamin B12. Thus, severe deficiency can result in the presence of debilitating neurologic complications.²⁴ Laboratory findings to confirm these types of anemias are decreased serum vitamin B12 levels and IF, normal folate levels, and increased serum methylmalonic acid and total homocysteine levels.⁸

Once vitamin B12 deficiency anemia has been confirmed, early treatment is important since neurological sequelae can be irreversible if not treated in a timely manner. Treatment options include replacement therapy in a variety of dosage forms, most commonly intramuscular or oral formulations. Generally, parenteral replacement is the preferred method since approximately 10% of these doses are absorbed compared to only 0.5-4% of oral doses.²² For this reason lower doses of vitamin B12 can be given when administered intramuscularly. In order for oral therapy to be effective, high doses must be given. Table 3.1 contains recommended dosing for both oral and parenteral vitamin B12 therapies.^{22, 24}

Lab values and symptoms should be monitored to determine response to therapy. Neurological symptoms and megaloblastic cells should resolve within a few days, in general. An increase in H/H should be noted after about one to two weeks of therapy.²⁴ Replacement therapy is usually long term for patients without pernicious anemia. For those diagnosed with pernicious anemia, lifelong therapy will be required.²² CBC and serum vitamin B12 levels should be monitored over time, at least 1-2 months after initiation of therapy and 3-6 months thereafter.^{22,24} Side effects of replacement therapy include dizziness, headache, anxiety or nausea.²⁵ Increased consumption of foods rich in vitamin B12 can help alleviate deficiency and prevent future episodes. Meat, fish, poultry, eggs and dairy products are examples of these. As noted previously, increased consumption of nutrients such as this can be difficult for vegetarians and prophylactic dietary supplementation may be indicated.22

Folic Acid Deficiency Anemia:

Folic acid deficiency anemia is another common type of anemia in the United States. This macrocytic anemia is caused by diet, alcoholism, pregnancy and lactation, and dialysis. Folic acid deficiency can also be drug-induced and may be due to the use of sulfasalazine, methotrexate, phenytoin, triamterene, or trimethoprim.^{3,8,10}

Unique signs and symptoms of folic acid deficiency are irritability, personality changes, and memory impairment.¹⁷ Refer to Table 2.1 for additional symptoms. Confirmation of this deficiency anemia is obtained by lab values of decreased folate levels, and normal vitamin B12, IF and methylmalonic acid levels.¹⁰ Treatment of this anemia is usually accomplished with oral replacement therapy. Table 3.2 describes common dosing regimens for folic acid deficiency anemia. Side effects of replacement therapy are generally mild and include malaise, rash and flushing.²⁶ Green leafy vegetables, citrus fruits, dairy and grains are examples of dietary sources rich in folate.¹⁷

Normocytic Anemias

Acute Blood Loss Anemia:

Hemorrhage and acute blood loss results in anemia due to RBC volume depletion. Acute blood loss can occur with GI bleeds, trauma or surgery. Symptoms of acute blood loss are rapid blood pressure decline and dizziness.⁵ This is categorized as a normocytic anemia since the existing RBCs are largely unaffected. Hemoglobin and Hematocrit (H/H) are surrogate makers for this type of anemia. An elevated reticulocyte count in also noted in these patients.¹⁷ Refer to Table 1.3 for normal values of these labs. Treatment for acute blood loss anemia is generally a blood transfusion if the loss is substantial, in addition to stopping the source of the bleed.⁵

Chronic Blood Loss Anemia:

Anemia in chronic blood loss results from a slow downward trend of RBC volume. Conditions such as stomach ulcers, diverticulitis, cancers or heavy menstrual bleeding are associated with this type of anemia. Symptoms include fatigue, shortness of breath or paleness.⁵ Lab values are similar to those of acute blood loss and display decreased H/H values.¹⁷ Treatment with blood transfusions for this type of anemia may not be indicated; however supplementation with iron therapy may be used for several months.⁵

Aplastic Anemia:

Aplastic anemia occurs when a bone marrow disorder results in a decreased production of RBCs. Other causes of this type of anemia include radiation and chemotherapy, exposure to toxins, autoimmune disorders, HIV, Epstein-Barr virus, parvo and pregnancy.¹² Some medications may also cause aplastic anemia such as phenytoin, carbamazepine, chloramphenicol, felbamate and quinine.¹⁷ Symptoms of this type of anemia include fatigue, rapid or irregular heart rate, frequent infections, unexplained bruising, nosebleeds and bleeding gums, and rash.¹² Lab values for aplastic anemia show decreased reticulocyte count, white blood cells (WBCs) and platelets.¹⁷ For a confirmatory diagnosis a bone marrow biopsy is required. Blood transfusions, stem cell transplant or pharmacotherapies are treatments for this type of anemia.¹² Immunosuppresants such as cyclosporine, methylprednisolone, or antithymocyte globulin are examples.¹² Bone marrow stimulants including filigrastim and epoetin alfa can also be used as adjunctive therapy with immunosuppresants.¹² Therapy with antivirals and antibiotics may be warranted to prevent infections in these vulnerable patients.

Anemia of Chronic Kidney Disease:

Patients with chronic kidney disease often exhibit anemia due to decreased production of erythropoietin by the kidneys. These patients often suffer from weakness, inability to concentrate, chest pain, fatigue, and headache.¹¹ Heart failure and tachycardia are common complications of this type of anemia.¹¹ Decreased reticulocyte count and normal or increased WBCs and

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platelets are often seen in this patient population.¹⁷ Additional testing may include H/H, ferritin and TSAT levels.^{11,17} Common treatments involve erythropoietin, iron supplementation, blood transfusions, and vitamin B12 and folate supplementation.¹¹

Other Anemias

Another form of anemia is anemia of chronic disease. Also called "anemia of inflammation", this disorder is due to conditions such as rheumatoid arthritis, lupus, cancer, HIV, and inflammatory bowel disease.²⁷ When severe, this type of anemia resembles iron deficiency anemia.²⁷ Symptoms are general, see Table 1.2 for a list. Suspected cases of this type of anemia are generally confirmed by detection of an increased level of cytokines. Other lab values include decreased MCV and TIBC, increased TSAT, and normal/elevated serum iron and ferritin.^{17,27} Treatment options for anemia of chronic disease include blood transfusions, erythropoietic agents, and iron therapy if deficiency is present.²⁷

There are several other types of anemia which are less common. Two examples of these are sickle cell anemia and myeloplastic anemia which will not be discussed in the article.

Pharmacist's Role

The pharmacist has a critical role in the treatment of patients with anemia. Pharmacists can assist patients with therapy management, particularly in areas of iron administration, dietary recommendations, drug interactions with oral iron, and medications that can exacerbate conditions. As pharmacists, we should also be aware of the signs and symptoms of anemia in order to assess efficacy of treatment and refer those patients who need to seek medical attention. Pharmacists can utilize their extensive pharmacological knowledge to increase positive outcomes in our patients.

Acute	Chronic
Tachycardia	Asymptomatic
Palpitations	Fatigue
Angina	Weakness
Hypotension	Headache
Light-headedness	Sensitivity to cold
Shortness of breath	Pale and yellow skin
"Whooshing" sound in ears	

Table 1.2. General signs and symptoms of anemia.

CBC		Iron Studies		RBC Indices		Other	
Hgb	M: 14-17 g/dL	Serum Iron	M: 46-160 mcg/dL	MCV	80-100 fL/cell	Vitamin B12	180-660 pg/mL
	F: 12-15 g/dL		F: 30-160 mcg/dL				
Hct	M: 42-50% F: 36-45%	Serum Ferritin	12-300 ng/mL	MCH	27-33 pg/cell	Plasma Folate	3.4-12.4 mcg/L
RBC count	M: 4.5-6 x 10 ⁶ cell/mL	TIBC	220-420 mcg/dL	MCHC	33.4- 35.5%	Reticulocyte	M: 0.5-1.5%
	F: 4-5 x 10 ⁶						F: 0.5-2.5%
	cell/mL	TSAT	30-50%			RBC distribution width	14.5-15.5%
						Schilling test (intrinsic factor)	10% excretion of radiolabeled B12
						Methylmalonic acid	0.08-0.56 mcmol/I
						Homocysteine	4-17 mcmol/L
CBC=i Hgb=h Hct=h RBC=i M=ma F=fem TIBC= TSAT: MCV= MCH=	complete blood coun emoglobin ematocrit red blood cell le	t pacity on in	lboratory paramete	ers and non	mal ranges.		

Iron Deficiency	Vitamin B ₁₂ Deficiency	Folate Deficiency
Sore mouth	Numbness/parasthesia	Irritability
Smooth tongue	Imbalance (gait disturbance)	Personality changes
Pica	Personality changes	Depression
Pagophagia	Swollen/inflamed tongue	Memory impairment
Reduced saliva	Depression	Mouth sores

Chronic Conditions	Drug-induced	Miscellaneous	Agent	Percent Elemental Iron	Elemental Iron/Dose Form		
Crohn's Disease	Aspirin	Folic acid deficiency	Ferrous gluconate	12%	39 mg/325 mg tablet		
Ulcerative colitis	NSAIDS	Vitamin B12 deficiency			37 mg/300 mg tablet		
Rheumatoid Arthritis	PPIs	Pregnancy	Ferrous sulfate	20%	65 mg/325 mg tablet	Decrease iron absorption	Medications affected by
Autoimmune disorders	H ₂ RAs	Lactation			60 mg/300 mg tablet	Decrease from absorption	iron
Cancer	Antacids	Heavy menstruation			44 mg/5 mL elixir	Gastric acid suppressants	Levodopa/methyldopa
Liver disease	Trimethoprim	Reduced stomach acid	Ferrous fumarate	33%	33 mg/100 mg tablet	(antacids, PPIs)	Levothyroxine
Thyroid disease	Triamterene	Poor diet				Cholestyramine	ž
Chronic Kidney Disease	Methotrexate	Malnutrition	Polysaccharide-iron complex	100%	150 mg/capsule		Bisphosphonates
Dialysis	Phenytoin	Infection	•		50 mg/tablet	Tetracycline/doxycycline	
Alcoholism	Sulfasalazine	Children	Table 2.2. Oral iron pro	oducts.			Fluoroquinolones
Table 1.1. Risk factors for anemia. PPIs=proton pump inhibitors H ₂ RAs=histamine 2 receptor antagonists						Table 2.3. Drug-drug interacti	Tetracycline/doxycycline

Anemia

Agent	Recommended Dosing
Iron sucrose	Non-dialysis: 200 mg administered on 5 different occasions within 14 days totaling 1000 mg in 14 days
Iron dextran	Dose (mL) = 0.0442 (desired Hgb - observed Hgb) x LBW + (0.26 x LBW), with desired hemoglobin at 14.8 g/dL and LBW= lean body weight; test dose of 0.5 ml should be given
Sodium ferric gluconate	125 mg elemental iron per dialysis session. Most patients will require a cumulative dose of 1 g elemental iron over approximately 8 sequential dialysis treatments to achieve a favorable response
Ferric carboxymaltose	<50 kg: 15 mg/kg elemental iron on day 1; repeat dose after at least 7 days (maximum: 1500 mg elemental iron per course). May repeat course of therapy if anemia reoccurs
	${\geq}50$ kg: 750 mg on day 1; repeat dose after at least 7 days (maximum: 1500 mg per course). May repeat course if anemia reoccurs

Table 2.4. Parenteral iron products.

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Agent	Dosing	Adverse Drug Reactions
Vitamin B ₁₂ :		
Oral B ₁₂	1000-2000 mcg/day	Nausea, nervousness, dizziness, headache edema, itching, diarrhea, rhinitis, dysnpea peripheral vascular thrombosis, avoid if
IM B ₁₂ injections	Start with 8-10 loading	allergic to cyancobalamin or cobalt
	doses of 1000 mcg several times 1 week (if severe), taper to 1000 mcg /month	

Table 3.1. Recommended dosing for vitamin E IM=intramuscular

Agent	Dosing	Adverse Drug Reactions
Folate:		
Folic acid	Adults: 0.4 mg/day	Malaise, flushing, rash, erythema,
(PO, IV, IM, SQ)	Pregnancy: 0.8/day	bronchospasm

Table 3.2. Recommended dosing for folate.

PO=oral IV=intravenous IM=intramuscular

IM=intramuscular SQ=subcutaneous

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ACPE UAN# 0100-0000-14-069-H01-P 0100-0000-14-069-H01-T

