Anemia Assessment

30

Christine A. Hughes

Chapter Objectives

1. Describe the classification of anemia.
2. Complete a patient assessment and interpret laboratory findings to determine the most likely cause of anemia.
3. Apply a monitoring and follow-up plan for patients initiated on treatment for anemia.

Background

Anemia is commonly encountered in clinical practice and is characterized by a decrease in hemoglobin (Hgb) or red blood cells (RBCs) resulting in reduced oxygen carrying capacity of the body [1] . Anemia is defined by the World Health Organization as a Hgb < 130 g/L in adult men, <120 g/L in non-pregnant adult women, and <110 g/L in pregnant women [2]. Severe anemia is a Hgb < 80 g/L in adult men and non-pregnant women [2]. It is important to note that Hgb values vary based on gender as well as ethnicity. As examples, women typically have lower Hgb concentrations than men, and African-Americans have lower values as compared to Caucasians [1].

Anemia can cause significant morbidity and mortality. Older adults with anemia have higher hospitalization and mortality rates, while anemia in children can impair cognitive and psychomotor development. Globally, anemia impacts approximately 25% of the world population [1]. In the United States, estimates suggest almost 6% of the population has anemia, with certain groups such as the elderly or pregnant women at higher risk [3].

Given the prevalence of anemia, pharmacists play an important role in assessing patients with anemia, determining potential cause(s), and identifying the need for additional laboratory testing or referrals where appropriate. Pharmacists can also assist patients with treatment options, dietary recommendations, and managing drug-drug interactions with oral iron supplements.

Clinical Presentation

Sign and symptoms of anemia can vary considerably depending on factors such as the rate of development and overall health status of the patient [4]. In many cases, mild anemia is asymptomatic and may be found when ordering a complete blood count (CBC) as part of routine bloodwork or other investigations [1]. In patients that are otherwise healthy, signs or symptoms may not be obvious even at low Hgb concentrations if the anemia develops slowly

C. A. Hughes (✉)
University of Alberta, Faculty of Pharmacy and Pharmaceutical Sciences, Edmonton, AB, Canada
e-mail: Christine.hughes@ualberta.ca

S. H. Mahmoud (ed.), *Patient Assessment in Clinical Pharmacy*,
https://doi.org/10.1007/978-3-030-11775-7_30

Table 30.1 General signs and symptoms of anemia

Symptoms	Signs
Fatigue	Pale skin or mucous membranes
Weakness	Tachycardia
Dizziness or lightheadedness	Palpitations
Headache	Shortness of breath on exertion

over time [4]. In anemias that develop very rapidly, symptoms tend to be more pronounced. Because hemoglobin delivers oxygen, signs and symptoms are often related to lack of oxygen delivery including fatigue, weakness, dizziness, or shortness of breath. Cardiac signs or symptoms may include chest pain, palpitations, or tachycardia. On examination, patients may exhibit pallor of skin and/or mucous membranes. In the elderly, signs and symptoms of anemia may overlap with other causes and include increased falls, reduced cognition, and overall physical decline [1]. Depending on the cause of the anemia, patients may have additional symptoms related to underlying nutritional deficiencies such as neurologic symptoms as a result of vitamin B12 deficiency. General signs and symptoms of anemia are summarized in Table 30.1.

Etiology

Anemia occurs when there is an imbalance in the production and destruction or loss of RBCs. There are three primary causes of anemia: blood loss, inadequate RBC production, and increased RBC destruction [4]. Blood loss can be caused by acute (e.g., trauma) or chronic (e.g., gastrointestinal ulcers) bleeding. Nutritional deficiencies (B12, folate, iron), chronic kidney disease, thyroid disease, liver disease, bone marrow failure, and anemia due to chronic disease or inflammation can lead to inadequate RBC production. Increased destruction of RBCs may be caused by hereditary (e.g., sickle cell anemia, thalassemia) or acquired (e.g., immune hemolytic anemia) conditions.

Approach to the Assessment of Anemia

Anemia reflects an underlying disease or condition; therefore, it is important to conduct a thorough work-up to determine the cause in order to guide appropriate management. Laboratory tests should be evaluated in the context of the patient history and physical examination to diagnose anemia. Laboratory tests also play an important role in assessing response to treatment.

History and Physical Examination

A detailed patient history may provide clues as to the cause of the anemia [1]. Specific questions to ask the patient may depend on the situation as well as laboratory tests that are available.

- *Signs of blood loss* – Consider blood loss from the gastrointestinal (GI) tract, genitourinary tract, or as a result of trauma. A menstrual history should be taken for women to rule out heavy menstrual bleeding.
- *Past medical history* – Chronic conditions associated with anemia include: rheumatoid arthritis, systemic lupus erythematosus, chronic kidney disease, congestive heart failure, liver disease, thyroid disease, hemolytic disorders, aplastic anemia, certain cancers (e.g., leukemia, lymphoma), infections (e.g., human immunodeficiency virus, tuberculosis, osteomyelitis), inflammatory bowel disease, celiac disease.
- *Surgeries or procedures* – Recent surgeries may cause anemia or result in secondary bleeding. Gastric bypass surgery can lead to reduced absorption of vitamins. A history of recent blood donation should also be considered.
- *Medications* – Drugs may cause or contribute to anemia through different mechanisms. For example, non-steroid anti-inflammatory drugs (NSAIDS), anticoagulants, and antiplatelet agents may promote bleeding and iron deficiency. Certain chemotherapy or antimalarial agents, zidovudine, trimethoprim,

Table 30.2 Common laboratory tests used to diagnose anemias

Test	Reference range[a]	Description
Complete blood count		
Red blood cells (RBCs)	(Males) 4.5–6.0 × 10^{12}/L (Females) 4.0–5.6 × 10^{12}/L	–
Hemoglobin (Hgb)	(Males) 137–180 g/L (Females) 120–160 g/L	Amount of hemoglobin in a unit of blood
Hematocrit (Hct)	(Males) 0.40–0.54 (Females) 0.36–0.48	Percentage volume of RBCs in the blood
Mean corpuscular volume (MCV)	82–100 fL	Size of the average RBC
Mean corpuscular hemoglobin concentration (MCHC)	320–360 g/L	Average concentration of Hgb in the RBC
Red cell distribution width (RDW)	11–16%	Measures variation in RBC volume
Iron studies		
Serum iron	(Males) 8–30 µmol/L (Females) 6–28 µmol/L	Measures iron bound to transferrin
Total iron binding capacity (TIBC)	40–80 µmol/L	Measures iron binding capacity of transferrin
Transferrin saturation index	0.15–0.50	Ratio of serum iron to TIBC expressed as a percent
Ferritin	(Males) 30–400 µg/L (Females) 13–375 µg/L	Indicator of iron body stores. Caution interpreting ferritin in the presence of inflammatory conditions or malignancy
Others		
Vitamin B12	155–700 pmol/L	–
Folate – Serum	>12.0 nmol/L	–
Reticulocyte count	40–100 × 10^{9}/L	Immature RBCs

[a]Example adult reference ranges obtained from Calgary Laboratory Services. Accessed May 29, 2018. Available at http://www.calgarylabservices.com/lab-services-guide/lab-tests/

sulfasalazine, phenytoin, phenobarbital, metformin, and proton pump inhibitors may cause macrocytic anemias. Ribavirin, and less commonly select antibiotics, NSAIDS, and other agents can cause hemolytic anemia.

- *Diet* – Dietary history may suggest possible deficiencies such as B12, folate, or iron in the diet.
- *Family history* – This may be useful to identify potential inherited anemias, such as thalassemia or sickle cell disease.
- *Pregnancy* – Women that are pregnant have increased iron demands and are at a higher risk of iron deficiency anemia.

In addition to general signs of anemia on physical examination, there may be additional findings that are suggestive of specific causes [1]. For example, jaundice or scleral icterus may be a sign of hemolytic anemia. Patients with B12 deficiency may experience altered mental status or numbness and tingling in their hands and feet. Iron deficiency anemia can cause brittle nails and a smooth or swollen tongue.

Laboratory Tests

Common laboratory tests used for diagnosis of anemias include the complete blood count (CBC), reticulocyte count, iron studies, and vitamin B12 and folate levels [1]. A summary of these laboratory tests and what they measure is found in Table 30.2. Decreased Hgb or RBC count confirms that the patient has anemia. However, it is important to recognize that Hgb and Hct may decrease when plasma volume increases (fluid overload) and may increase when plasma volume decreases (dehydration) [5]. Evaluating trends in Hgb (chronic versus more recent onset) as well as absolute values in the context of the patient history can provide useful information.

The next step is to look at mean corpuscular volume (MCV) in order to categorize the anemia

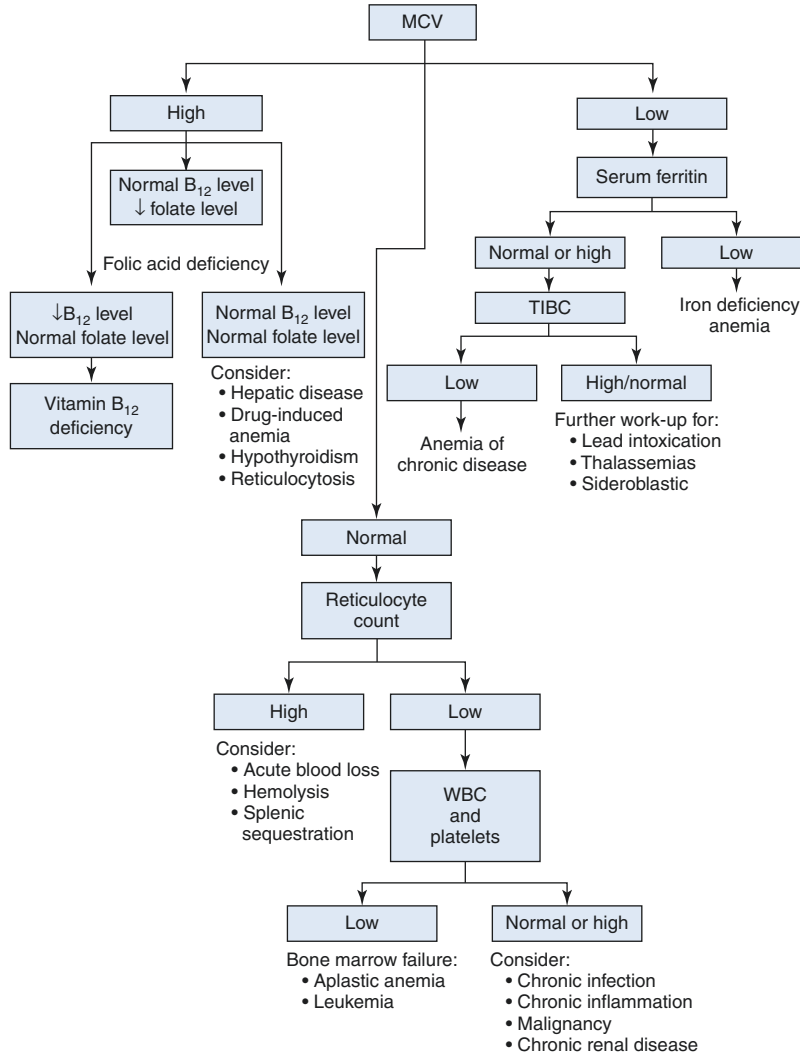

Fig. 30.1 General algorithm for diagnosis of anemias. Reprinted by permission from McGraw-Hill Education. BJ Wells, JT DiPiro, TL Schwinghammer, CV Dipiro. *Pharmacotherapy Handbook*, Tenth Edition

and narrow down potential causes. An algorithm for assessing anemia based on MCV is found in Fig. 30.1. Anemias are commonly classified as microcytic (MCV < 82 fL), macrocytic (MCV > 100 fL), or normocytic (MCV 82–100 fL). MCV represents a measurement of the average size of RBCs, and therefore can sometimes be misleading in patients with mixed anemias. For example, MCV may appear normal in patients who have both anemia of chronic disease and iron deficiency anemia. In some cases, the red cell distribution width (RDW) may provide additional information. A normal RDW indicates homogeneity in RBC size, whereas an increased RDW indicates variation in RBC size. A peripheral smear may be ordered to examine the size and shape of RBCs as well as abnormal circulating cells [1].

In patients with microcytic anemia, iron studies are needed to differentiate the cause. A low serum ferritin is usually the best indicator of iron deficiency anemia. Because serum ferritin reflects iron stores in the body, ferritin decreases even before the anemia develops [5]. However, ferritin is an acute-phase protein and is therefore elevated by inflammation. In this situation, a ferritin level greater than 100 μg/L suggests iron deficiency is unlikely [5]. Other iron studies, including serum iron, total iron binding capacity (TIBC), and transferrin saturation are often not that helpful in

Table 30.3 Laboratory differentiation of iron deficiency anemia (IDA) and anemia of chronic disease (ACD)

Test	IDA	ACD	IDA + ACD
Mean corpuscular volume (MCV)	↓	Normal or ↓	Normal or ↓
Red cell distribution width (RDW)	↑	Normal	↑
Serum iron	↓	↓	↓
Total iron binding capacity (TIBC)	↑	Normal or ↓	Normal or ↓
Transferrin saturation	↓	Normal or ↓	↓
Ferritin	↓	Normal	Normal

distinguishing iron deficiency anemia from anemia of chronic disease [5]. A trial of iron therapy may be necessary to confirm the diagnosis. RDW is often increased in iron deficiency anemia as smaller microcytic cells are formed. Table 30.3 compares laboratory test results in patients with iron deficiency anemia and anemia of chronic disease.

Normocytic anemia can have a number of different causes and further investigations are often needed [1]. The reticulocyte count can be useful in differentiating potential causes of normocytic anemia. A high reticulocyte count suggests the bone marrow is functioning appropriately in response to the anemia and thus potential causes may include acute blood loss or hemolysis. In the case where hemolytic anemia is suspected, additional useful tests may include lactate dehydrogenase, haptoglobin, or a Coombs test [1]. In patients with a normocytic anemia and a low reticulocyte count, potential causes may include bone marrow failure or chronic infection, inflammation, malignancy or chronic kidney disease. Evaluation of other blood cells (white blood cells and platelets), serum creatinine, liver tests as well as consideration of the patient's history and physical examination will aid in narrowing down the cause.

Assessing macrocytic anemias should include reviewing medications that the patient is taking, as well as any history of alcohol use to determine whether these may be implicated in causing the anemia [1]. Zidovudine, chemotherapy drugs, and hydroxyurea are common causes of macrocytic anemia. To rule out nutritional deficiencies, vitamin B12 and serum folate levels should be ordered. Low serum folate levels suggest folate deficiency; however, it is important to note that serum folate levels are relatively nonspecific and can change rapidly with dietary restriction [1]. Dietary deficiency of folate is generally uncommon as a result of foods fortified with folic acid in many countries, however decreased absorption of folate or increased demands (e.g., pregnancy) can result in deficiency. Deficiency in vitamin B12 is caused by low dietary intake or more frequently, poor absorption. A falsely low B12 level may be seen during pregnancy and in women taking oral contraceptives [1]. A vitamin B12 level <150 pmol/L is suggestive of deficiency. However, vitamin B12 levels at the lower end of the reference range may be associated with clinical symptoms of B12 deficiency and would therefore require treatment.

Management and Follow-Up Assessment

Management of the anemia depends on the cause as well as the patient's clinical status. For example, in anemia of chronic disease, the anemia is often corrected by treating the underlying disease. Specific treatment of the various types of anemia is beyond the scope of this chapter. However, treatment and follow-up assessment of iron, folic acid, and vitamin B12 deficiency are briefly summarized below.

Once the diagnosis of iron deficiency anemia and the underlying cause has been determined, treatment is often initiated with oral iron supplements. Patients may be encouraged to increase dietary intake of foods rich in heme iron (e.g., lean red meats, fish) or non-heme iron (e.g., legumes, tofu) [6, 7]. Ascorbic acid (vitamin C) increases absorption of non-heme iron, whereas tannins found in tea and coffee can decrease absorption. For oral iron supplements, the usual target dose is 100–200 mg of elemental iron per day in divided doses [6]. Common iron supplements as well as their elemental iron content are summarized in Table 30.4 [6]. For maximum absorption, oral iron should be

Table 30.4 Comparison of oral iron supplements

Iron supplement	Elemental iron	Usual maximum dose (adults)
Ferrous gluconate 300 mg tablet	35 mg	Two tablets three times daily
Ferrous sulfate 300 mg tablet	60 mg	One tablet three times daily
Ferrous fumarate 300 mg tablet	100 mg	One tablet two times daily
Heme-iron polypeptide (e.g., Proferrin®) 11 mg tablet	11 mg as heme iron	One tablet three times daily
Polysaccharide-iron complex (e.g., Feramax®) 150 mg capsule	150 mg	One capsule once daily

administered on an empty stomach, 1 h before or 2 h after a meal. Administration of oral iron supplements with a glass of orange juice can improve absorption. Side effects commonly encountered with oral iron supplements are abdominal pain, nausea, constipation, diarrhea, metallic taste, and dark stools [6]. If patients are having difficulty tolerating oral iron, management strategies may include starting with a lower dose of elemental iron and titrating slowly, switching to a preparation with a lower amount of elemental iron, or administering iron with small snacks or meals. There are a number of drug-drug interactions with iron supplements to be aware of including antacids, proton pump inhibitors, H2-antagonists, and tetracycline or doxycycline that can decrease iron absorption. In addition, iron can impact the absorption of levodopa, levothyroxine, fluoroquinolones, bisphosphonates, integrase strand transfer inhibitors, tetracycline, and doxycycline; therefore, administration times should be separated [8]. To assess response to treatment, a CBC should be ordered approximately 4 weeks after starting therapy [6, 7]. Hgb is expected to increase >10 g/L after 4 weeks of treatment [6]. Iron deficiency anemia usually corrects within 2–4 months of starting therapy if appropriate doses are used and the underlying cause is corrected. However, oral iron is recommended to be continued for about 3 months after Hgb normalizes in order to replenish iron stores. A serum ferritin should be ordered to confirm repletion of iron stores prior to discontinuing therapy.

Folate deficiency is treated with folic acid supplementation. The dose of folic acid used and duration depends on the cause of the deficiency; however, common doses for treatment are 1–5 mg orally per day [9]. Recommended intake of folic acid in adults through diet and supplements is 400 μg/day. The United States Preventive Services Task Force recommends women planning or capable of pregnancy take a daily supplement of 400–800 μg/day [10]. Foods that are rich in folic acid include green leafy vegetables, citrus fruits, and grains. It is important that vitamin B12 deficiency is ruled out prior to starting folic acid, as folate may correct the anemia but does not treat the neurologic manifestations of vitamin B12. CBC should be repeated at approximately 1 month to assess response to treatment. Usually, Hgb normalizes within 2 months. Folate level should be repeated in approximately 3–4 months.

B12 deficiency can be treated with oral or parenteral vitamin B12 [9]. The decision to use oral versus parenteral initially may depend on the cause of the anemia (e.g., malabsorption), the severity, and presence of neurologic symptoms. High dose oral vitamin B12 (1–2 mg/day) has been shown to be as effective as intramuscular administration in terms of correcting the anemia and neurologic symptoms [11]. However, parenteral vitamin B12 may be preferred until B12 levels are corrected in those with neurologic symptoms as well as patients who are nonadherent to oral B12 therapy. There are a number of dosing schedules for parenteral vitamin B12 [12]. For patients with dietary deficiency, lower doses of vitamin B12 can be used (e.g., 250 μg/day) [12]. Patients with pernicious anemia or any B12 deficiency caused by malabsorption require lifelong therapy [9]. CBC and vitamin B12 level should be repeated 1–2 months after initiation of therapy to ensure correction.

Clinical Pearls

- Investigation of the underlying cause of the anemia is necessary.
- MCV categorizes anemia into microcytic, normocytic, and macrocytic.
- In mixed anemias, MCV may be misleading – assessing MCV along with RDW (and/or the peripheral smear) may be helpful to identify mixed anemias.
- Reticulocytes can help categorize anemias as hypo- or hyper-proliferative.
- Pharmacists play an important role in assessing patients with anemia and monitoring response to treatment.

References

1. Vieth JT, Lane DR. Anemia. Emerg Med Clin North Am. 2014;32:613–28.
2. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva: World Health Organization; 2011. (WHO/NMH/NHD/MNM/11.1) Available at: http://www.who.int/vmnis/indicators/haemoglobin.pdf (accessed May 29, 2018).
3. Le CHH. The prevalence of anemia and moderate-severe anemia in the US population (NHANES 2003-2012). PLoS One. 2016;11(11):e0166635. https://doi.org/10.1371/journal.pone.0166635.
4. Cascio MJ, DeLoughery TG. Anemia: evaluation and diagnostic tests. Med Clin N Am. 2017;101:263–84.
5. Kujovich JL. Evaluation of anemia. Obstet Gynecol Clin N Am. 2016;43:247–64.
6. Toward Optimized Practice Iron Deficiency Anemia Committee. Iron deficiency anemia clinical practice guideline. Edmonton: Toward Optimized Practice; 2018. Available from: http://www.topalbertadoctors.org (accessed May 30, 2018).
7. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anemia. Lancet. 2016;387:907–16.
8. CPS [Internet]. Iron preparations: oral. Ottawa: Canadian Pharmacists Association; 2018. (updated November 2017; cited May 30, 2018). Available at: http://www.myrxtx.ca.
9. Green R, Mitra AD. Megaloblastic anemias: nutritional and other causes. Med Clin North Am. 2017;101:2979–317.
10. U.S. Preventive Services Task Force. Folic acid for the prevention of neural tube defects: U.S. preventive services task force recommendation statement. Ann Intern Med. 2009;150:626–31.
11. Langan RC, Goodbred AJ. Vitamin B12 deficiency: recognition and management. Am Fam Physician. 2017;96:384–9.
12. CPS [Internet]. Vitamin B12. Ottawa: Canadian Pharmacists Association; 2018. (updated July 2012; cited May 30, 2018). Available at: http://www.myrxtx.ca.