REVIEW ARTICLE

AN OSTEOPATHIC APPROACH TO ANEMIA

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KEYWORDS:

Anemia

Folate deficiency

Iron deficiency anemia

Vitamin B12 deficiency

Abstract

With close to 2 billion people affected globally, anemia is a commonly seen condition worldwide. Diagnosed by a patient's low hemoglobin, and then subsequently differentiated through red blood cell indices, a complete blood count should be performed on every patient presenting with the classic symptoms of anemia. Iron studies, as well as the corrected reticulocyte count and peripheral blood smears, can also be of use to further specify the exact type of anemia. Additionally, tests including colonoscopies, upper endoscopies and gynecologic procedures should be considered to identify the different underlying causes of the disease. The most common microcytic anemias include iron deficiency, thalassemia and anemia of inflammation. Deficiencies in folate and B12—also known as cobalamin—are the most common etiologies of macrocytic anemia. Treatment of each of these types of anemia is tailored to the individual patient based on the severity of their condition as well as the specific underlying cause. Osteopathically, anemia falls largely into the respiratory-circulatory model, as well as the metabolic-energy model, which can also be used to guide treatment. For a family physician, identifying symptoms, making accurate diagnoses and properly treating patients with anemia is of the utmost importance.

INTRODUCTION

Anemia can be broadly defined as any condition that results in a deficiency of red blood cells (RBCs) or a decreased amount of hemoglobin, an iron-rich protein that binds oxygen. Anemia causes decreased oxygen delivery to tissues and can result in symptoms including lethargy, dyspnea, weakness and pallor. Anemia impacts approximately one-third of the world's population.[1] Estimations of the global prevalence suggest that 1.93 billion people are affected by anemia with iron deficiency being the most prominent cause, contributing to more than 60% of cases.[1] Other common causes include nutritional deficiencies, such as folate and B12, and conditions that result in prolonged inflammation. Understanding this complex etiology is crucial for the diagnosis and management of anemia.

Risk factors for anemia include female sex, increased age, nutritional deficiencies, heavy menstruation and pregnancy.[2] Anemia can develop by means of ineffective erythropoiesis, hemolysis and blood loss.[3] Though anemia can be classified by its cause, it is typically differentiated based upon the size, shape and color of RBCs. Hemoglobin levels that fall below given thresholds in both men and women are indicative of anemia. These thresholds, established by the World Health Organization, are 12 g/dL in women and 13 g/dL in men.[4,5]

COMMON ETIOLOGIES

Iron deficiency anemia (IDA) is most often a result of conditions such as malabsorption, gastrointestinal bleeding and heavy menstrual periods.[5,6] Folate and B12 deficiencies, which interrupt DNA synthesis, are grouped under megaloblastic anemia. B12 deficiency is common in malabsorptive states, such as malnutrition. Folate deficiency is most often seen in alcoholism, malnutrition and states of increased folate requirement, such as pregnancy. Non-megaloblastic anemias include deficiencies that are not due to a breakdown in DNA synthesis, such as liver disease and cancer.[7] Anemia of inflammation (AI), previously known as anemia of chronic disease, is caused by underlying conditions which result in a decrease in RBC synthesis or an increase in RBC loss.[8,9] Table 1 highlights various underlying causes of AI.

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 Print ISSN: 1877-573X
doi:10.33181/13085

TABLE 1:

Potential causes of anemia of inflammation[8–12]

Infection (viral, bacterial, parasitic, fungal)
Rheumatoid arthritis
Systemic lupus erythematosus
Inflammatory bowel disease
Sarcoidosis
Vasculitis
Chronic kidney disease
Chronic inflammation
Chronic rejection post organ transplant
Malignancy

CLINICAL MANIFESTATIONS

General symptoms are common among all anemias and are seen due to the body's lack of oxygenated blood resulting from reduced hemoglobin levels. These symptoms include fatigue, dizziness, lightheadedness, dyspnea, exercise intolerance, weakness, palpitations, headache and difficulty concentrating.[13] Often, these symptoms appear when hemoglobin levels fall below 7.0 g/dL, though comorbidities, the duration of anemia and its underlying etiology have a significant impact as well.[14] Symptoms specific to each type of anemia can be determined based on their underlying etiology as shown in Table 2.

TABLE 2:

Clinical manifestations of anemia[5,13–20]

	UNIQUE SYMPTOMS/SIGNS	SPECIAL CONSIDERATIONS
IDA	Pica Restless leg syndrome Brittle integument Cheilosis Spooning of the fingernails	Symptoms can occur prior to a change in the patient's hemoglobin level.
B12	Loss of proprioception Loss of vibratory senses Areflexia Irritability Acute psychosis Gait abnormalities	Gait abnormalities can be in the form of sensory ataxia that manifests as a positive romberg sign.
Folate	None	None

DIAGNOSTIC WORKUP

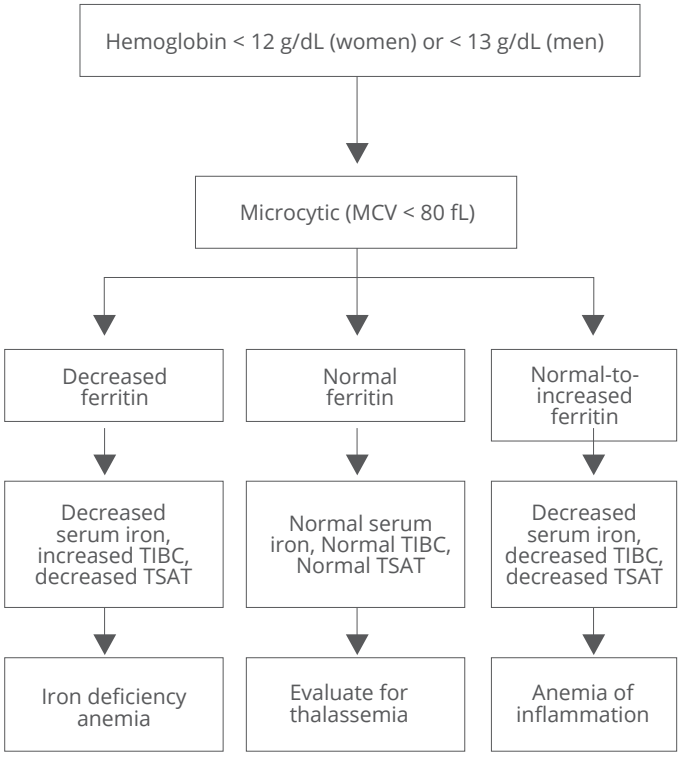
The initial workup of anemia is commonly done through the evaluation of hemoglobin concentration. A hemoglobin value indicative of anemia can only diagnose anemia and cannot determine the exact cause. Once established, the mean corpuscular volume (MCV) is assessed, which categorizes the anemia as microcytic (<80 fL), normocytic (80–100 fL) or macrocytic (>100 fL), which then allows for a more tailored evaluation.[21]

Microcytic

Once the anemia has been determined to be microcytic, iron studies—which include serum iron, ferritin, total iron binding capacity (TIBC) and transferrin saturation (TSAT)—are conducted. Figure 1 outlines the lab values that are used to further differentiate the 3 common causes of microcytic anemia.

FIGURE 1:

Diagnostic algorithm for microcytic anemia [23,26,27]



Ferritin levels, which serve as a measure of iron stores, below 45 µg/mL and above 100 µg/L are associated with IDA and AI, respectively.[9] Traditionally, a threshold of under 15 µg/mL can diagnose IDA, but a concentration of less than 45 µg/mL has a higher sensitivity with only a mild decrease in specificity.[22] The upregulation of ferritin, noted in AI, is due to ferritin being an acute-phase protein whose secretion is promoted by inflammatory mediators.[9,23] However, the inflammatory cytokines of AI reduce the levels of transferrin. The functional capacity of transferrin to bind iron is represented by the TIBC. The transferrin saturation, which is calculated by dividing serum iron by the TIBC, will be low in both IDA and AI.[18,24]

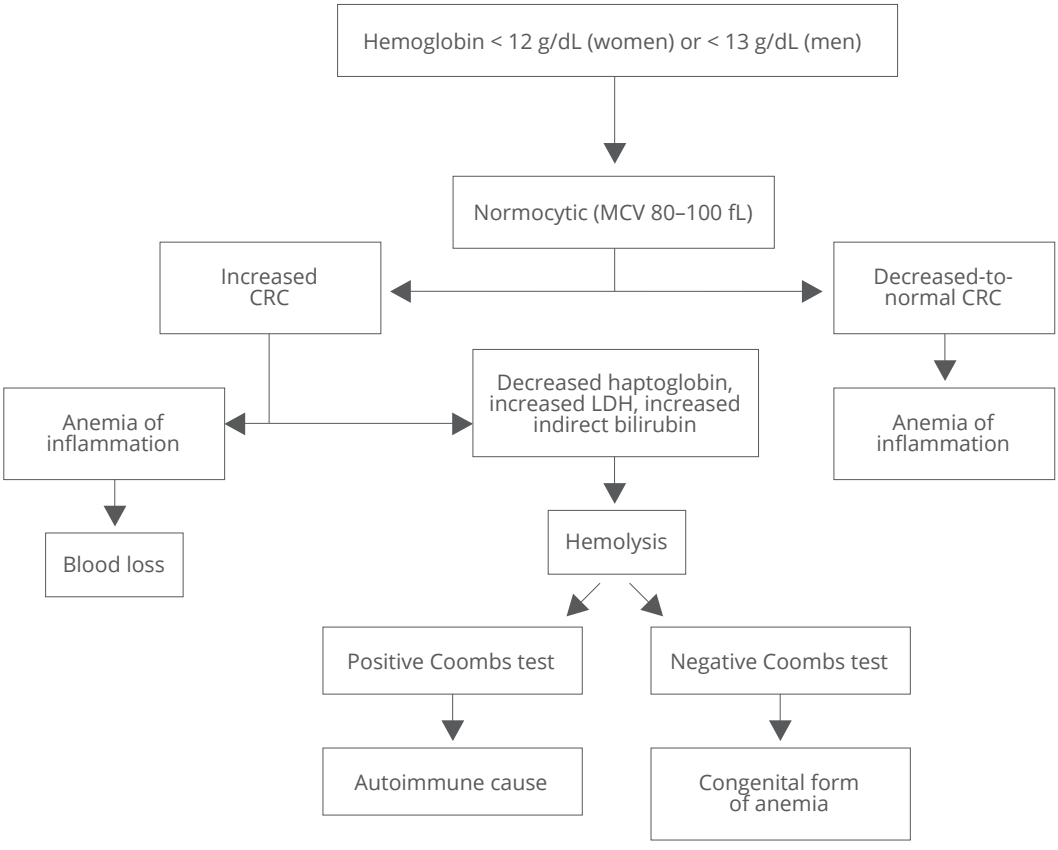
If all iron studies are normal, then thalassemia should be part of the differential diagnosis. Thalassemia can be further differentiated by hemoglobin electrophoresis. The Mentzer index, which is calculated by dividing the MCV by the RBC count, helps differentiate thalassemia from IDA. A Mentzer index value of <13 is indicative of thalassemia.[23,25]

Normocytic

When the MCV is within 80–100 fL, the corrected reticulocyte count (CRC)—also known as the reticulocyte index—and peripheral blood smear are then evaluated to find the root cause of the anemia. Typically, normocytic anemia is further subdivided by the CRC, which is derived from the reticulocyte count. The CRC adjusts for the degree of anemia and better reflects the state of erythropoiesis.[18,28] A decreased CRC is indicative of an inadequate bone marrow response to the anemia.[28] Though AI can be found in microcytic anemia, it is commonly the cause of normocytic anemia with a decreased or normal CRC.[9,13,18,29] Alternatively, an elevated CRC implies increased RBC turnover due to blood loss or hemolysis.[23] Hemolysis is supported with labs of increased indirect bilirubin, decreased haptoglobin and increased lactate dehydrogenase, and hemolysis can be further subdivided into congenital or acquired by a Coombs test. To determine the etiology of the hemolysis, a peripheral blood smear should be completed.[24] Figure 2 illustrates the lab evaluation for normocytic anemia.

FIGURE 2:

Diagnostic algorithm for normocytic anemia [13,27,29]

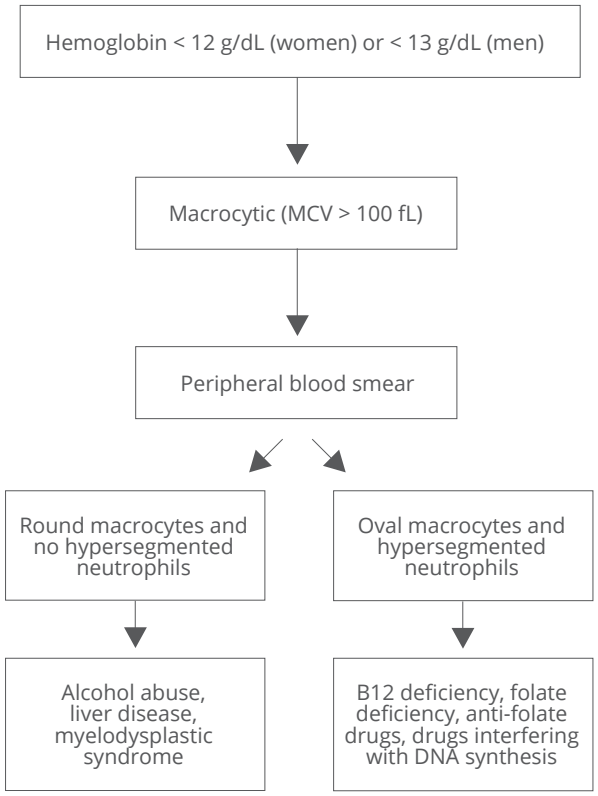


Macrocytic

Macrocytic anemia is subdivided into megaloblastic and non-megaloblastic anemias based on a peripheral blood smear. Hypersegmented neutrophils and macro-ovalocytes will be found with megaloblastic anemia, while morphological abnormalities are not present with non-megaloblastic anemia.[18,24] Serum homocysteine and methylmalonic acid levels can be obtained to further differentiate between folate or B12 deficiencies. Only homocysteine levels will be increased with folate deficiency, whereas both homocysteine and methylmalonic acid will be elevated in B12 deficiency.[18] Figure 3 highlights the workup for macrocytosis.

FIGURE 3:

Diagnostic algorithm for macrocytic anemia [21,27]



TREATMENT

Treatment of anemia is guided by the underlying cause. Oral iron therapy is typically prescribed for patients diagnosed with nutritional IDA. Ferrous salts are the standard first line oral iron therapy because of their high bioavailability, cost effectiveness, and accessibility.[5,30,31] Among the ferrous iron compounds, their side effects, bioavailability and efficacy are similar though their elemental iron content varies as shown in Table 3. The recommended daily dose of elemental iron for IDA patients is 150–200 mg.[18] It is recommended to avoid consumption of inhibitors of iron absorption such as whole grains, legumes, tea, coffee, red wine, hot chocolate, as well as proton pump inhibitors and antacids.[5,30] Common side effects with iron supplementation include metallic taste, epigastric pain, nausea, vomiting, constipation and dark stools.[16,21]

TABLE 3:

Oral iron therapy for iron deficiency anemia [5,30,31]

ORAL IRON FORMULATION	DOSE PER TABLET	ELEMENTAL IRON PER TABLET	SPECIAL CONSIDERATIONS
Heme Iron Polypeptide	398 mg	11 mg	Can be taken with food Acidic environment not required for absorption
Ferrous Gluconate	240 mg 325 mg	27 mg 38 mg	Best absorbed on empty stomach
Ferrous Sulfate	325 mg	65 mg	Best absorbed on empty stomach
Ferrous Fumarate	325 mg	106 mg	Best absorbed on empty stomach
Polysaccharide Iron Complex	150 mg	150 mg	Can be taken with food Acidic environment not required for absorption

In 2019, the FDA approved ACCRUFeR®, a new oral iron therapy for adults with IDA. This ferric maltol based compound represents a comparably efficacious and well-tolerated alternative for those who experience treatment-limiting intolerance issues such as nausea, abdominal discomfort, and constipation.[32,33] Other advancements in the treatment of IDA include Injectafer®, a ferric carboxymaltose based compound that offers an alternative parenteral option for treating patients who are refractory to or cannot tolerate conventional oral iron therapy.[34]

Treatment options for B12 deficiency anemia include supplementation with either 1 mg intramuscular (IM) injections or 1–2 mg oral formulations[19]. Dosing schedule and duration depend on the patient's symptomatic state as well as the underlying cause of the deficiency. If the patient's underlying cause is reversible and the patient is without severe neurologic symptoms, then dosing 3 times per week is warranted.[19] In cases with severe neurologic deficits, the frequency of dosing should increase to every other day.[19] For patients with a reversible condition, such as a nutritional insufficiency, supplementation should be discontinued following a resolution of symptoms or a correction of deficiency, whichever occurs first.[19] If the cause of deficiency is irreversible, such as malabsorption, then the treatment continues indefinitely.[19] Oral supplementation is non-inferior to IM injections throughout the first 8 weeks of treatment. After 8 weeks, IM injections were found to be superior.[35]

Folate deficiency anemia is generally treated with oral folate supplementation due to the underlying cause of the deficiency

typically being a lack of dietary intake. Folic acid, the oral supplement for folate replacement, is dosed up to 5 mg per day. The duration of treatment continues until resolution of the anemic state or until the underlying cause of the deficiency is addressed. If the cause of the deficiency is irreversible, such as a malabsorptive state, then treatment continues indefinitely.[11,14]

AI and macrocytic non-megaloblastic anemias are treated by controlling the underlying cause of disease or by removing the offending agent. Referral to hematology may be considered in some circumstances.

OTHER STUDIES

Given that anemia is a disease of multiple potential etiologies, numerous evaluative techniques can be performed to find the root cause for each patient. Determining the underlying cause, such as folate, B12 or iron deficiencies, or malabsorption is key to coordinating treatment. Beyond those already mentioned, other studies should be considered to evaluate the various causes. Since IDA can be due to blood loss, either gross or occult, further work-up should include evaluations of the gastrointestinal tract with both colonoscopy and upper endoscopy.[36] If neither evaluation identifies the cause, small bowel investigation is warranted. In women, heavy menstrual bleeding is a common cause of IDA.[37] Pelvic ultrasonography, saline infusion ultrasonography and hysteroscopy can be used to screen for common causes of heavy menstrual bleeding, such as endometrial polyps, intracavitary lesions or adnexal lesions.[38]

OSTEOPATHIC CONSIDERATIONS

Anemia primarily involves the metabolic-energy and respiratory-circulatory osteopathic models. This model aims to restore optimal function of metabolic processes while replenishing energy loss and fatigue due to ineffective metabolism.[39] Including more leafy green vegetables, for example, can help prevent recurrence of iron-deficiency anemia. There have been numerous studies conducted investigating the relationship between veganism, Mediterranean diets, and anemia.[40,41] Veganism is frequently associated with the development of mineral deficiencies, and it is even recommended that vegans should also receive B12 supplements regularly.[42]

The respiratory-circulatory model aims to restore vascular, gaseous and lymphatic movement.[39] It is understood that nutrition and blood flow create an environment that can facilitate or impede organ function.[19] The circulation absorbs nutrients from our diets and is distributed systemically. An anemic state can markedly disturb this circuit.

A significant consequence of anemia is fatigue. The CV4 technique increases parasympathetic activity and decreases sympathetic activity. For this technique, with the patient supine, the physician cradles the occipital bone laterally while easing the cranium into extension. This results in a decrease in sleep latency, thus improving fatigue.[43]

Occipitoatlantal decompression is another technique used to increase parasympathetic activity.[44] For this treatment, with the patient supine, the physician's fingers balance the patient's head at the occipital condyles. The physician then applies a superior tractional force, decompressing the condylar region.[45]

CONCLUSION

Anemia continues to affect a widespread population around the world. While various treatments have been instituted, investigation remains both about the origins of the disease and its pathophysiology. Due to its multifaceted etiologies, anemia remains elusive in terms of its root causation in many patients. Continued studies of micronutrients could be analyzed to further manage this disease state. Increasing awareness of appropriate nutrition and lifestyle habits will help to alleviate the burden of anemia.

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