LABORATORY TESTING FOR ANEMIA

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INSTRUCTIONS FOR USE

Physician Decision Support (PDS) is a lab ordering tool operated by BeaconLBS. This Clinical Guideline supports the Questions and Answers that appear in PDS for tests referenced in this document. UnitedHealthcare reserves the right, in its sole discretion, to modify its Clinical Guidelines as necessary. This Clinical Guideline is provided for informational purposes. It does not constitute a Medical Policy or medical advice.

GUIDELINES

For laboratory testing to determine the etiology of anemia (low hemoglobin), BeaconLBS recommends that reticulocyte count is always the next step.

- If there is evidence of microcytosis, BeaconLBS recommends reticulocyte count, serum iron, total iron-binding capacity, serum ferritin, and thyroid-stimulating hormone (TSH) level to be performed.
- If there is evidence of macrocytosis, BeaconLBS recommends reticulocyte count, vitamin B12, folate, and TSH level to be determined.
- If the anemia is not associated with microcytosis or macrocytosis, BeaconLBS recommends a reticulocyte count, CBC with differential and platelet count, serum ferritin, serum iron, total iron-binding capacity, TSH level, folate, and vitamin B12 to be performed.

If the anemia is hyperproliferative (i.e., the reticulocyte count is high), then parameters of hemolysis should be obtained (i.e., serum total bilirubin, LDH, and haptoglobin).

These recommendations are based upon laboratory diagnostic approaches for anemia in major medical textbooks including Netter’s Internal Medicine, Textbook of Critical Care, Goldman’s Cecil Medicine, Henry’s Clinical Diagnosis and Management by Laboratory Methods, and Harrison’s Principles of Internal Medicine.
Anemia is a public health problem that impacts all countries and all stages of life. Globally, approximately 1.62 billion people (24.8% of the population) are affected by anemia.\textsuperscript{1} While the US has a smaller percentage of affected individuals, anemia is still one of the most frequent causes of medical visits because of the prevalence in children, women of reproductive age, and elderly people, especially if poor nutrition is present.\textsuperscript{2} Moreover, anemia is one of the leading signs in many diseases or is the first evidence of disease observed in routine blood cell enumeration.\textsuperscript{2}

Anemia is defined as a reduction in the total number of red blood cells (RBCs) or amount of hemoglobin in the circulation.\textsuperscript{3} The World Health Organization (WHO) has established reference ranges for normal blood hemoglobin concentrations, depending on age and gender.\textsuperscript{1,2} Anemia is present if the blood concentration of hemoglobin falls below 13.0 g/dL (130 g/L) in men or below 12.0 g/dL (120 g/L) in women.\textsuperscript{1,2}

As the primary function of RBCs is to deliver oxygen to the tissues, anemia results in impaired oxygen delivery and consequently, tissue hypoxia.\textsuperscript{3} Signs and symptoms may include:

- Fatigue, dyspnea, syncope, or impairment of organ function due to decreased oxygen
- Pallor or postural hypotension due to decreased blood volume
- Palpitations, onset of heart murmurs, or congestive heart failure due to increased cardiac work

Anemia is not a diagnosis, but is a sign of underlying disease. Most anemias have a specific etiology.\textsuperscript{4} More than 100 diseases may cause anemia, but 90% belong to one of 3 groups: nutritional deficiencies (e.g., iron, vitamin B12, or folic acid), anemia of chronic disease (ACD; e.g., chronic inflammation, chronic renal insufficiency, or tumors), and bleeding.\textsuperscript{2} Reticulocyte count is often used as an indicator of production of new red blood cells and bone marrow.\textsuperscript{3}

When narrowing down the cause of anemia, 3 other aspects are helpful in the evaluation:

- Determination of acuity of the anemia (i.e., acute, subacute, or chronic) and whether it is progressive or stable; results of previous complete blood counts (CBCs) should be obtained
- Determination whether the bone marrow response to the anemia is appropriate (hyperproliferative) or inadequate (hypoproliferative); reticulocyte count should be obtained
- Review erythrocyte morphology on peripheral blood smear (e.g., for hypochromia or abnormally shaped red blood cells)

The Complete Blood Count (CBC) should be the first test performed when anemia is a possibility. A hemoglobin level of less than 13 g/dL in men or less than 12 g/dL in women warrants further evaluation for the presence of anemia.\textsuperscript{1,2} A CBC often includes:\textsuperscript{3,4}

- Red blood cell (RBC) count
- White blood cell (WBC) count
- Total blood hemoglobin
- Fraction of blood composed of RBCs (hematocrit)

A CBC may also include: \textsuperscript{3,4}
Morphological Classification

Anemia can be categorized morphologically on the basis of MCV, as follows:\(^4\)

- Microcytic (MCV <80 μm\(^3\) or fl)
- Normocytic (MCV 80–100 μm\(^3\) or fl)
- Macrocytic (MCV >100 μm\(^3\) or fl)

Anemia and overt or subclinical hypothyroidism are frequently co-morbid conditions.\(^5-7\) In patients with hypothyroidism, anemia may be microcytic (e.g., due to achlorhydria or chronic blood loss), normocytic (e.g., due to decreased erythropoietin levels), or macrocytic (e.g., due to associated pernicious anemia).\(^6\)

In a recent publication, Tefferi, et al. listed many of the diagnostic possibilities for patients with anemia.\(^8\) Within this article the categories of anemia (microcytic, normocytic, and macrocytic) are subdivided by differential diagnosis that is determined using both CBC and peripheral blood smear results. Similarly, the 6th edition of the Textbook of Critical Care by Vincent, et al., highlights the differential diagnosis of anemia using the CBC and reticulocyte count as a starting point.\(^9\) Vincent, et al., splintered the differential diagnoses using the index of ≥2.5, which includes those disorders resulting in hemolysis or hemorrhage, and <2.5.\(^9\) Within the index <2.5, the diagnosis is further evaluated using red blood cell morphology into normocytic, normochromic (hypoproliferative) and micro- or macrocytic (maturation disorder).

**Microcytic Anemia**

When a patient presents with a microcytic anemia, there are three main diagnostic possibilities: iron deficiency anemia (IDA), hemoglobinopathies (e.g., thalassemia), and anemia of chronic disease (ACD).\(^2,8\) Sideroblastic anemia is another rare possibility, but is usually not considered unless the patient has a history of lead exposure.\(^2\) Microcytic anemias have low MCV values and often low MCHC. Microscopic examination reveals small and often pale red cells.\(^9-11\) The RDW can distinguish thalassemia and ACD from IDA; patients with thalassemia or ACD usually have normal RDW, whereas those with IDA have increased RDW.\(^2\)

Globally, the most common anemia is that in patients with IDA and it is assumed that 50% of anemia cases are due to iron deficiency.\(^4\) The main risk factors for IDA are low iron intake, poor absorption of iron, and periods of life when iron requirements are high.\(^4\) In patients with IDA, the progression of laboratory abnormalities is a loss of stainable bone marrow iron, a decrease in the serum ferritin level, a decrease in the serum iron content and n increase in total iron-binding capacity, anemia, a decrease in MCV, increasing poikilocytosis, and hypochromia.\(^12\) Microcytic anemia is also thought to result from insufficient production of hemoglobin.\(^12\)

**Macrocytic Anemia**

Macrocytic anemia is generally drug-induced or caused by a nutritional deficiency.\(^8\) The use of certain drugs (examples: hydroxyurea or HIV medications) or alcohol can predispose a patient to macrocytic anemia and should...
be initially ruled out. Nutritional deficiencies, such as folate or vitamin B12, and poor nutritional intake or absorption are other potential causes of macrocytic anemia.  

Both folate and vitamin B12 are associated with the thymidine synthesis pathway, so these deficiencies cause defective RNA and DNA synthesis. As a result, nuclear maturation may be arrested and lead to macrocytic RBCs in patients with these deficiencies. Additionally, neutrophils and platelets may also be defective; neutrophils are often hypersegmented in these patients.

If drug- or nutrition-related causes are ruled out, macrocytic anemia should be investigated on the basis of a peripheral blood smear for megaloblastic features. The MCV in the macrocytic anemias is increased, and large, oval cells (macro-ovalocytes) are seen. Megaloblastic features and marked MCV (>110 fl) are often associated with primary bone marrow disease (e.g., myelodysplastic syndrome [MDS]).

Normocytic Anemia

Normocytic anemias may be caused by any of the following:

- Decreased production of normal-sized RBCs (e.g., ACD or aplastic anemia)
- Increased destruction or loss of RBCs (e.g., hemolysis or posthemorrhagic anemia)
- Uncompensated increase in plasma volume (e.g., pregnancy or fluid overload)
- Co-existing microcytic and macrocytic anemias

Anemia of chronic disease encompasses a variety of conditions, including inflammatory conditions, infections, neoplasms, and other systemic disorders. It is the most common cause of normocytic anemias and the second most common form of anemia worldwide (after IDA). Generally, ACD is caused by hypoactivity of the bone marrow, insufficient production of erythropoietin, poor response to erythropoietin, or shortened RBC survival duration. Endocrine deficiency, such as hypothyroidism, and renal failure can also be associated with a decrease in the production of RBCs.

Hemolytic anemias are characterized by increased destruction or loss of RBCs and can be congenital or acquired. Congenital hemolytic anemias include hemoglobinopathies, RBC membrane disorders, and RBC enzyme deficiencies. Acquired hemolytic anemias include autoimmune hemolytic anemias, mechanical hemolysis, and paroxysmal nocturnal hemoglobinuria. Bleeding or hypersplenism can also cause an increased loss of RBCs.

Examination of a peripheral blood smear is essential in normocytic anemias to determine reticulocyte count. It may also be important to evaluate iron and other nutritional markers because normocytic anemia has many potential causes.

Correction of Anemia

Anemia can be corrected by treatment of the underlying disorder, blood transfusion, iron supplementation, erythropoietin administration, or a combination; for monitoring, hemoglobin level is preferred over hematocrit because it is more reproducible. In 2006, the National Kidney Foundation recommended correcting anemia to a hemoglobin level of 11.0-13.0 g/dL in patients with kidney disease, but recent data indicate that a lower target hemoglobin level may be preferred. A higher hemoglobin threshold (≥13.3 g/dL) may be associated with cardiac complications related to increased blood viscosity and possibly, ventricular overload in these
patients. In clinical trials, risk for mortality or morbidity did not differ significantly with lower (<12.0 g/dL) vs higher (>13.3 g/dL) hemoglobin targets in patients with chronic kidney disease or in infants with very low birthweights who received transfusions. Research in this area is ongoing. Ideal target hemoglobin levels may also vary with pregnancy, heavy menstruation, high altitude, smoking habits, males aged >70 years, non-Caucasian race, presence of chronic lung disease, or presence of hemoglobinopathy.

**CLINICAL EVIDENCE**

Because there are many causes of anemia, a selective diagnostic approach is recommended. After an anemia has been identified and categorized on the basis of MCV, more specific tests can determine the etiology. *Netter’s Internal Medicine*, describes a laboratory diagnostic approach for classification of anemia that includes using results from hemoglobin, hematocrit, MCV, morphology/blood smear, iron studies, serum B12, and folate.

**Reticulocyte Count**

The reticulocyte count is a simple and cost-effective test that is extremely useful for distinguishing anemias secondary to decreased red cell production from those caused by hemolysis. The reticulocyte count in normal individuals is about 1%, consistent with a red cell lifespan of approximately 120 days. An elevated reticulocyte count reflects the release of an increased number of young cells from the bone marrow.

**Evaluation of Iron Status**

Serum iron is a measure of iron that is bound to transferrin, while total iron-binding capacity is the amount of iron that would appear in the blood if all the transferrin was saturated with iron. The reference interval for serum iron is 50–160 μg/dL (9–29 μmol/L) in adults. The level is lower in iron deficiency and in infection and anemia of chronic disease. Total iron-binding capacity is an indirect measurement of transferrin concentration. The reference interval for adults is 250–400 μg/dL (45–72 μmol/L). In iron deficiency anemia, the serum TIBC is increased. It is normal or decreased in the anemia of chronic disease.

Transferrin saturation is serum iron divided by total iron-binding capacity (Fe / total iron-binding capacity). Normally, this is 20%–55%; values below 15% indicate iron-deficient erythropoiesis. Transferrin saturation is low in patients with iron deficiency and high in patients with iron storage diseases. Transferrin saturation of 5% or less has a positive likelihood ratio for iron deficiency of 16.5, while transferrin saturation of 6-8% has a positive likelihood ratio for iron deficiency of only 1.43. Transferrin is an acute phase reactant, so transferrin levels and transferrin saturation are affected by co-existing acute illnesses.

Serum ferritin is useful in the diagnosis of hypochromic, microcytic anemias. The levels of ferritin in serum correlate with total body iron stores and are therefore a suitable laboratory estimate of iron stores. In adults, the reference values are 12–300 μg/L, with higher values in men than in women. Serum ferritin appears to be in equilibrium with tissue ferritin and is a good reflection of storage iron in normal subjects and in most disorders. It is decreased in patients with iron deficiency anemia and increased in those with iron overload. Low serum ferritin (<18 μg/L) has a positive likelihood ratio for iron deficiency of >40, while a serum ferritin of 19-45 μg/L has a positive likelihood ratio for iron deficiency of about 3. Total iron stores are often evaluated by measuring serum ferritin, but like transferrin, ferritin is an acute phase reactant, so co-existing acute illness may skew serum ferritin levels.
Bone marrow studies are considered the “gold standard” for evaluation of iron status, but are invasive and expensive, and the results can vary with the examiner.\textsuperscript{20} Recently, a meta-analysis of 20 studies demonstrated that soluble transferrin receptor (sTfR) can improve the diagnosis of IDA as a surrogate to bone marrow studies, especially in patients with co-existing chronic disease or gastrointestinal malignancies.\textsuperscript{20}

**Microcytic Anemia**

The presence of small red cells (MCV <77 fl) indicates a defect in the production of hemoglobin.\textsuperscript{9-11} Serum marker studies including serum iron, total iron-binding capacity, and serum ferritin may be useful to diagnose a microcytic anemia. Serum iron can confirm diagnosis of IDA or hemochromatosis. Total iron-binding in the same specimen may distinguish between iron deficiency and other disorders. Tefferi, et al. outlined the diagnostic algorithm for microcytic anemia which starts with determination of serum ferritin.\textsuperscript{8}

**Macrocytic Anemia**

A modest increase in red cell size is encountered in a variety of conditions, including liver disease, hypothyroidism, acute blood loss, hemolytic anemia, aplastic anemia, and alcoholism.\textsuperscript{9-11} Macrocytic anemia can be further described with the determination of folate and vitamin B12 levels. Folic acid deficiency is common in pregnant women, alcoholics, patients with diets that lack raw fruits and vegetables, and people with gastrointestinal structural damage. The most reliable and direct method of diagnosing folate deficiency is to determine folate levels in both serum and erythrocytes.\textsuperscript{2} Low folic acid levels can also be the result of dietary deficiency or result from a primary vitamin B12 deficiency that decreases folic acid uptake. Vitamin B12 is decreased in patients with pernicious anemia, total or partial gastrectomy, elderly age, malabsorption, and certain congenital biochemical disorders.

Vitamin B12 has normal serum levels range from 118–148 pmol/L (160–200 ng/L) to \textasciitilde{}738 pmol/L (1000 ng/L). In patients with megaloblastic anemia due to cobalamin deficiency, the level is usually <74 pmol/L (100 ng/L).\textsuperscript{11} Folic acid has a normal range is from 11 nmol/L (2 mg/L) to \textasciitilde{}82 nmol/L (15 mg/L). The serum folate level is low in all folate-deficient patients.\textsuperscript{11} It also reflects recent diet. Because of this, serum folate may be low before there is hematologic or biochemical evidence of deficiency.

**Normocytic Anemia**

When neither microcytosis nor macrocytosis is present in a patient with anemia, it may be helpful to consider co-existing microcytic anemia and macrocytic anemia. Often, such an anemia panel would consist of a CBC with differential and platelet count, reticulocyte count, serum ferritin, folate (folic acid), iron, total iron-binding capacity, and vitamin B12. Tefferi, et al.\textsuperscript{8} outlines the diagnostic algorithm for normocytic anemia which starts with ruling out treatable causes such as nutritional anemia, hemolytic anemia, and anemia of renal insufficiency.\textsuperscript{8} Further testing including serum ferritin, homocystein, serum creatinine, and hemolysis indicators should be performed depending on the suspected cause of the anemia.\textsuperscript{8}

**US FOOD AND DRUG ADMINISTRATION (US FDA)**

The FDA offers guidance and must approved many of these in vitro diagnostic assays.
There are several CMS policies that apply to the use of the tests that make up an anemia panel. In many cases, the test is reimbursable only when an appropriate diagnosis on the claim documents the medical necessity for the test. Reimbursement may also be restricted to a certain number of tests per year for the same recipient by the same provider, unless medical justification is documented.

Medicare does not pay for screening procedures (tests) performed in the absence of signs or symptoms. (Section 1862(a)(7) of the Social Security Act.

**APPLICABLE CODING**

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