

Evaluation of Anemia



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KEYWORDS

• Anemia • Iron deficiency • Hemolysis • Thalassemia • Vitamin B₁₂ • Macrocytosis

KEY POINTS

- The degree of macrocytosis may simplify the differential diagnosis of macrocytic anemia. An MCV >110 is characteristic of vitamin B₁₂ and folate deficiency, myelodysplasia, and certain medications.
- The evaluation of macrocytic anemia should include testing for vitamin B₁₂ and folate deficiency. An elevated methylmalonic acid level is the most specific test for B₁₂ deficiency. Homocysteine levels are high in B₁₂ and folate deficiency.
- Iron deficiency (low ferritin) precedes the development of anemia. A normal hemoglobin excludes anemia but does not rule out iron deficiency.
- Thalassemia trait is associated with mild or no anemia and more marked microcytosis than iron deficiency, which does not result in microcytosis until the Hb fall to less than 10 g/dL.
- Laboratory evidence of hemolysis includes an increased reticulocyte count, LDH, indirect bilirubin, and low haptoglobin level. The combination of an elevated LDH and low haptoglobin level is highly sensitive for hemolysis.

GENERAL CONSIDERATIONS

Anemia is a common problem encountered in primary care, occasionally discovered on routine testing. In clinical practice, anemia is defined as a reduction in hemoglobin (Hb) or hematocrit (Hct) obtained as part of a complete blood count (CBC). In general, red blood cell (RBC) associated measurements are lower in women compared with men. Anemia is often defined as Hb values that are more than 2 SD below the mean^{1,2}: men, Hb less than 13.4 g/dL; and women, Hb less than 12 g/dL. These definitions have several limitations. Normal Hb levels vary not only with sex but also with ethnicity.¹ Because the normal range is defined as the mean \pm 2 SD, then 2.5% of normal adults have values greater than 2 SD below the normal range and are diagnosed with anemia. An individual's Hb or Hct may also decline substantially from prior baseline values without falling below the normal reference range.

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It is also important to recognize that Hb, Hct, and RBC counts are concentrations that depend on RBC mass and plasma volume. Hb and Hct values decline when plasma volume increases (hemodilution) and are higher if plasma volume decreases (hemoconcentration). For example, patients with anemia who are volume depleted may have near normal Hb and Hct values on initial testing because of hemoconcentration. The underlying anemia becomes apparent only after normal volume status is restored.

Automated cell counters also measure the mean cell volume (MCV) and the red cell distribution width (RDW), an estimate of the variation in cell size. A normal RBC has a volume of 80 to 96 fL and is approximately the size of a nucleus of a small lymphocyte on a peripheral blood smear. An increased RDW indicates a substantial variation in RBC size but is not diagnostic of a particular disorder.

The MCV is a key parameter for classification of anemia. The first step in the evaluation of anemia is to classify it as macrocytic (MCV >100 fL), microcytic (MCV <80 fL), or normocytic (MCV 80–100 fL). This narrows the differential diagnosis of possible causes and directs further evaluation. The next step is to determine if the anemia is new or a long-standing problem. Recently diagnosed anemia is usually an acquired disorder, whereas a lifelong history of anemia is more likely to be an inherited disorder, especially if accompanied by a family history. Review of the electronic medical record may determine when the Hb began to fall and when the RBC indices began to change.

MACROCYTIC ANEMIA

Macrocytic anemias are characterized by an MCV greater than 100 (Box 1). The severity of the macrocytosis may simplify the differential diagnosis. A marked macrocytosis (MCV >110 fL) is characteristic of vitamin B₁₂ and folate deficiency, primary bone marrow disorders (myelodysplasia), and the use of certain medications. In contrast, a mild macrocytosis (MCV 100–110 fL) is more characteristic of alcohol abuse, liver disease, marked reticulocytosis, and hypothyroidism.

Box 1

Causes of macrocytic anemia MCV >100

- Vitamin B₁₂ deficiency
- Folate deficiency
- Medications
 - Hydroxyurea
 - Methotrexate
 - Imatinib
 - Anticonvulsants
 - Azathioprine
 - Nitrous oxide
- Primary bone marrow disorder
 - Myelodysplasia
 - Aplastic anemia
- Alcohol abuse
- Reticulocytosis
- Hypothyroidism

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