Anemia

Evaluation and Diagnostic Tests

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KEYWORDS

• Red cell indices • Schistocytes • Microcytic • Macrocytic • Cytogenetics • Anemia • Diagnostic testing

KEY POINTS

- Both the red cell indices and blood smear can offer clues to diagnosis and help to guide laboratory testing.
- Classification of anemia by either size of the red cell or mechanism (decreased production or increased loss) can narrow down the differential diagnosis.
- New molecular technologies may offer improved diagnostic sensitivity and specificity.

ANEMIA: DEFINITION

Although anemia is common, the exact cutoff to establish a diagnosis can be elusive. The standard definition is population-based and varies by gender and race. Current hemoglobin cutoff recommendations range from 13 to 14.2 g/dL in men and 11.6 to 12.3 g/dL in women.[1] Data from large population studies suggests that hemoglobin levels for African Americans tend to be 0.8 to 0.7 g/dL lower, perhaps owing to the high frequency of alpha-thalassemia in this population.[2] Another important factor is the trend of hemoglobin. For example, a patient with previous hemoglobin values at the higher end of the normal range, who now presents with a hemoglobin concentration at the lower end of the normal range, can now be considered anemic.

SYMPTOMS AND SIGNS OF ANEMIA

In general, the signs and symptoms of anemia are unreliable in predicting the degree of anemia. Several factors determine the symptomatology of anemia, with time of

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onset and overall baseline health of the patient being the most important. Patients who gradually develop anemia over a period of months can tolerate lower hemoglobin owing to the use of compensatory mechanisms. An example would be a patient with sickle cell disease who can tolerate a chronic hemoglobin concentration of 7 g/dL. Because blood delivers oxygen, many of the signs are related to lack of oxygen delivery, chiefly, fatigue and shortness of breath. On physical examination, anemia is manifested by paleness of the mucous membranes and resting tachycardia. One should look for other physical examination clues to a possible source of anemia, such as splenomegaly, guaiac-positive stools, or oral telangiectasia.

COMPENSATION FOR ANEMIA

There are 3 physiologic compensatory mechanisms for anemia. The first is by increasing cardiac output. Because oxygen delivery is cardiac output times hemoglobin, patients with decreased hemoglobin can maintain the same level of oxygen delivery by increasing cardiac output. Therefore, patients with limited cardiac reserve (heart failure, coronary artery disease) will have symptoms at higher hemoglobin concentrations than those with normal cardiac function. Increasing plasma volume is the second compensatory mechanism. This allows the remaining red cells to move around more efficiently owing to decreased viscosity. The increased plasma volume also increases cardiac output and helps to maintain blood pressure. Finally, red cell 2,3-diphosphoglycerate increases, which decreases oxygen affinity for hemoglobin. This results in more oxygen delivery to tissues. The high ambient oxygen tension in the alveoli leads to full oxygenation of hemoglobin despite its decreased oxygen affinity, but at the tissue level this results in more delivery of oxygen.

CLASSIFICATION

There are 2 classification systems for anemia (**Box 1**). The first is based on Wintrobe observations that red cell size can differentiate potential etiologies of anemia. This led to the concepts of "microcytic," "normocytic," and "macrocytic" anemia.[3] Microcytic anemias are those with a mean corpuscular volume (MCV) less than normal (<80 fL). Microcytic anemias reflect defects in hemoglobin synthesis. Lack of iron, either owing to deficiency or sequestration (anemia of inflammation), thalassemia, or sideroblastic anemias (defect of heme synthesis) all can lead to microcytosis.

There are 2 general etiologies of macrocytic anemias (MCV > 100 fL)[4]—red cell membrane defects and DNA synthesis defects. Red cell membrane defects can occur in the setting of liver disease or hypothyroidism. Macrocytic red blood cells (RBCs) in this setting tend to be round on review of the peripheral smear. In contrast, defects in DNA synthesis (such as those seen with megaloblastic anemia or chemotherapy) show a prominent oval macrocytosis. One of the most common causes of macrocytic anemia is the presence of a reticulocytosis. The average size of the reticulocyte (160 fL) can yield an high MCV in the setting of hemolysis.

The difficulty in using red cell size as a means of distinguishing potential etiologies for anemia is that, in many cases, the red cells demonstrate a normal size ("normocytic anemia," MCV 80–100 fL). This may occur during early stages of a process (such as iron deficiency) or when multiple processes occur simultaneously (concurrent iron deficiency and liver disease) and lead to a red cell size within the normal range.

The other classification schema uses the underlying mechanism of anemia (increase in RBC loss or decrease in RBC production). The first branch point is if red cell