The Evaluation and Classification of Anemia

A diagnostic approach

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Anemia is defined as hemoglobin concentration that is more than two standard deviations below the mean for age **(Table 1)**. Hemoglobin concentration varies considerably based on age and sex. Newborns have relatively high levels of hemoglobin due to intrauterine adaptation to a relatively hypoxic environment. During the first two months of life, hemoglobin production markedly decreases and a physiologic nadir occurs. The mean hemoglobin level rises gradually during childhood equally for boys and girls until puberty, when boys achieve a level approximately 20 percent higher than that of girls.

This article outlines the basic diagnostic approach to the evaluation of anemia.

PATHOPHYSIOLOGY OF ANEMIA

Anemia occurs as the result of one or a combination of four pathophysiologic mechanisms:

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- Acute blood loss (i.e., bleeding)
- Impaired production of red blood cells (i.e., iron deficiency, malignancy, aplasia)
- Increased destruction of red blood cells (i.e., immune-mediated hemolysis, hereditary spherocytosis, hemoglobinopathies)
- Sequestration of red blood cells within the spleen

HISTORY AND PHYSICAL EXAMINATION

The history and physical examination can assist in the evaluation of anemia and aid in determining the underlying etiology of anemia. Important components of the history and physical examination, as they pertain to the evaluation and diagnosis of anemia, are outlined below.

HISTORY

Pallor. A child with pallor is not necessarily anemic. Familial patterns of complexion are crucial because many patients are intrinsically pale. A careful evaluation of the child's medical history is fundamental in the assessment of a patient with suspected pallor.

Diet. The dietary history is very important when evaluating a patient for anemia. Infants delivered prematurely, or exclusively breastfed infants without adequate iron supplementation from solids in the second half of their first year of life are at risk for iron-deficiency anemia. Toddlers who consume large amounts of cow's milk and children and female adolescents who consume little meat are also at risk for iron-deficiency anemia. Patients and breastfed infants of mothers who follow a strict vegan diet may become deficient in vitamin B12.

History suggesting hemolysis. A neonatal history of hyperbilirubinemia supports a possible diagnosis of congenital hemolytic anemia such as hereditary spherocytosis. This can be further supported by a family history of anemia, splenectomy and/or cholecystectomy. Jaundice in a child of any age should prompt evaluation for hemolysis.

Medication and travel. Certain drugs, including antimalarial agents and sulfonamide antibiotics, can induce oxidant-associated hemolysis in the patient with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Other drugs can cause immune-mediated hemolysis (e.g., penicillin) or decreased red blood cell production (e.g., some anti-epileptic drugs). Travel history may suggest exposure to infections such as malaria.

PHYSICAL EXAMINATION

The general appearance of the child can provide clues to the severity and chronicity of the problem. Severe anemia that develops slowly over weeks or months, such as seen in iron deficiency, is often well-tolerated. Vital signs (including orthostatic blood pressure), height, weight and growth offer further insight into the severity and chronicity of the problem. Abrupt onset of anemia, such as is seen with acute blood loss or immune-mediated hemolytic anemia, can be associated with tachycardia and hypotension. Isolated pallor in a well-appearing child who does not have evidence of systemic disease is usually much less ominous than pallor noted in a child who is ill-appearing, has bruising, petechiae, lymphadenopathy and/or hepatosplenomegaly. Other clinical symptoms and physical exam findings that can be seen with anemia include: fatigue, headache, jaundice, tachycardia and flow murmur.

TABLE 1. Age-based norms for hemoglobin and MCV

AGE	HEMOGLOBIN (g/dL)	MCV (fL)
Newborn	16.5 (-2 SD 13.5)	108 (-2 SD 98)
2 months	11.5 (-2 SD 9.0)	96 (-2 SD 77)
3–6 months	11.5 (-2 SD 9.5)	91 (-2 SD 74)
6–24 months	12.0 (-2 SD 10.5)	78 (-2 SD 70)
2–6 years	12.5 (-2 SD 11.5)	81 (-2 SD 75)
6–12 years	13.5 (-2 SD 11.5)	86 (-2 SD 77)
12–18 years	Females 14.0 (-2 SD 12.0) Males 14.5 (-2 SD 13.0)	90 (-2 SD 78) 88 (-2 SD 78)

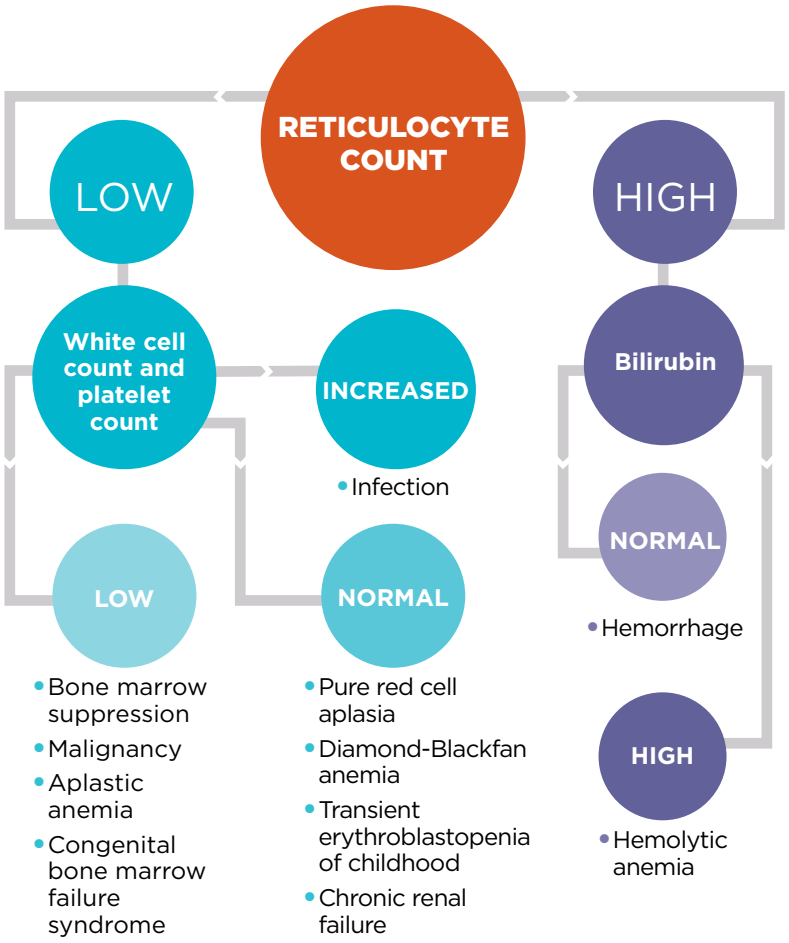
DIAGNOSTIC EVALUATION

The components of the initial workup for suspected anemia are outlined below. All of these components are key to the classification of the anemia.

CBC with differential. A complete blood count (CBC) should be the initial laboratory test in a child with suspected anemia. This should always include a white blood cell (WBC) differential and a peripheral smear (discussed below). Based on age-based norms **(Table 1)**, the presence or absence of anemia is then established. It is imperative to determine whether the patient has isolated anemia or if the anemia is accompanied by abnormalities in other cell lines (e.g., total WBC, neutrophils, lymphocytes, platelets). Anemia in combination with other cytopenias (e.g., thrombocytopenia, neutropenia) suggests a potentially more severe bone marrow disease.

Reticulocyte count. The reticulocyte count is essential to the classification of anemia. An elevated reticulocyte count indicates a bone marrow response to either increased red cell destruction (hemolysis) or acute or chronic blood loss. In cases of acute blood loss, there is a delay in bone marrow response of three to four days. Thus, in the setting of acute blood loss, the reticulocyte count is most helpful when the bleeding and subsequent anemia has been

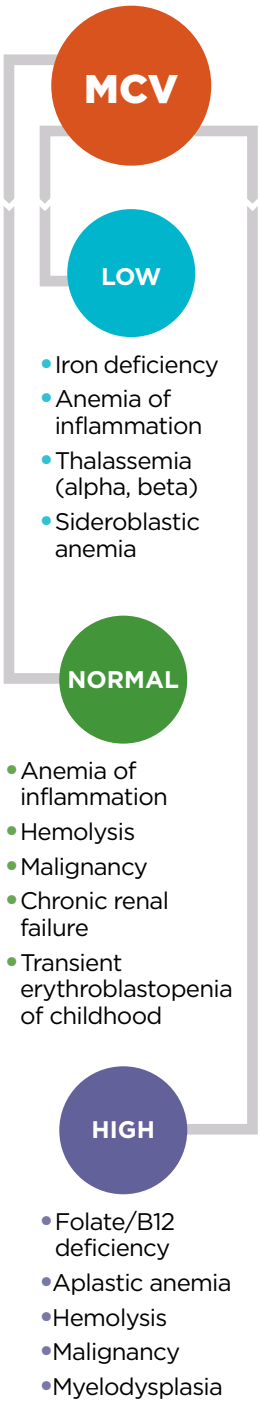
FIGURE 1. Framework for the classification of anemia based on reticulocyte count



New Physician Leader in Hematology/Oncology

Respected research leader **Cindy L. Schwartz, MD, MPH**, joined Children's Hospital of Wisconsin this year as medical director of Hematology/Oncology. She is also section chief of Pediatric Hematology and Oncology and a professor of Pediatrics at the Medical College of Wisconsin. After earning her medical degree at Brown University Program in Medicine, Dr. Schwartz completed a residency in Pediatrics and a fellowship in Pediatric Hematology/Oncology at Johns Hopkins University School of Medicine. She went on to earn a master's degree at Harvard School of Public Health. Dr. Schwartz brings her significant academic experience and expertise in the areas of Hodgkin lymphoma, osteosarcoma and childhood cancer survivorship to her new role at Children's. She is board-certified in Pediatrics and Pediatrics-Hematology/Oncology and is a member of the American Pediatric Society.

FIGURE 2.
Framework for the classification of anemia based on MCV



present for more than a few days. Anemias are classified on the basis of the adequacy of the reticulocyte response. The reticulocyte count is 1–2 percent in the setting of normal hemoglobin. In patients with moderate or severe anemia, the reticulocyte count may appear elevated, but may be inadequate for the degree of anemia. The following formula needs to be used to calculate the corrected reticulocyte count: (reticulocyte count x hemoglobin)/normal hemoglobin for age. If the corrected reticulocyte count is greater than 2 percent, the bone marrow is producing red blood cells at an accelerated pace. **Figure 1** displays a flow diagram that allows for the classification of anemia based on the reticulocyte response to the anemia.

Mean cell volume (MCV). The MCV reflects the red blood cell size and is vital to the classification of anemia. Normal standards for MCV are age-related **(Table 1)**; a simple guideline is that the lower normal limit of MCV for children older than 6 months of age is 70 fL plus the patient's age in years until the adult standard of 80–100 fL is reached. An elevated MCV is called macrocytosis and a low MCV is called microcytosis. Microcytosis is associated with iron deficiency, thalassemia, and long-standing anemia of inflammation. Macrocytosis is associated with vitamin B12 or folate deficiency, bone marrow failure syndromes (e.g., Fanconi anemia, Diamond-Blackfan anemia), and some cases of hypothyroidism. **Figure 2** displays a flow diagram that allows for the classification of anemia based on MCV.

Other abnormal cell lines. Evaluation of the total WBC count, differential, and platelet count is imperative in the setting of anemia. For example, leukopenia, neutropenia and/or thrombocytopenia occurring in a patient with anemia of underproduction is suggestive of aplastic anemia or infiltrative bone marrow disease such as leukemia. Thrombocytosis can occur in patients with iron deficiency, blood loss, inflammatory disease, infection, malignancy, or asplenia. Importantly, the interpretation of the etiology of anemia should not be done in isolation and should be considered within the context of the entire CBC.

Peripheral blood smear morphology. Abnormalities of red blood cell morphology are readily apparent upon peripheral blood smear review and provide clues to the etiology of anemia. For example, a predominance of spherocytic cells suggests hereditary sphercytosis or immune-mediated hemolytic anemia, whereas a predominance of small cells with exaggerated central pallor suggests iron deficiency anemia. The presence of immature leukocytes (i.e., blasts) associated with either a high or a low WBC count is suggestive of leukemia. Careful review of the peripheral blood smear by someone trained to evaluate cell morphology is crucial to the diagnostic evaluation of anemia.

Other laboratory abnormalities associated with anemia. Elevated indirect bilirubin, lactate dehydrogenase and aspartate aminotransferase levels are commonly seen in the context of hemolysis. Immune-mediated hemolytic anemia should be suspected when abrupt onset of anemia, jaundice, and/or reticulocytosis occur and spherocytes are seen on the peripheral smear. To investigate the etiology of hemolysis, a direct Coombs test to detect the presence of an autoantibody on the red blood cell surface should be done. A low serum iron level, elevated total iron-binding capacity, low percentage of iron saturation and decreased serum ferritin level support the diagnosis of iron deficiency. In the setting of chronic inflammation, the iron studies are often difficult to interpret since ferritin is an acute phase reactant. Hemoglobin identification should be completed to identify hemoglobinopathies such as sickle cell disease or thalassemia. Careful review of the newborn screen can also assist in the diagnosis of a hemoglobinopathy as the etiology of anemia. It is important to note that hemoglobin identification will be normal in patients with alpha-thalassemia trait; the presence of Bart's

hemoglobin on the newborn screen supports this diagnosis in a child with mild microcytic anemia and normal iron studies. Assessment of red blood cell enzyme levels (i.e., G6PD) is recommended when infection- or medication-related hemolytic anemia is suspected in a male of Mediterranean or African descent. Macrocytic anemia is concerning in children and should always trigger prompt assessment for vitamin B12 or folate deficiency in addition to potential bone marrow failure disorders. When other cytopenias are seen, such as thrombocytopenia and/or neutropenia in addition to anemia, bone marrow aspirate and biopsy should strongly be considered to rule out malignancy, aplasia or other bone marrow disorders.

CONCLUSIONS

In summary, anemia is a nonspecific finding. Various pathophysiologic mechanisms that result in anemia need to be elucidated by a careful and methodological workup. Indices easily obtained from a peripheral blood draw can be suggestive of these different pathophysiologic mechanisms. As discussed above and illustrated in **Figures 1 and 2**, the reticulocyte count and MCV are extremely important indices that should always be interpreted in the context of anemia, and are key to guiding additional diagnostic workup. The urgency of the workup and treatment is dependent upon the degree of anemia in combination with the suspected etiology. The summary of a suggested stepwise diagnostic approach to the evaluation and classification of anemia is outlined in **Figure 3**.

SPECIALTY SPOTLIGHT

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The MACC Fund Center at Children's Hospital of Wisconsin is one of the largest pediatric cancer and hematology programs in the country. Our interdisciplinary approach to diagnosis and treatment involves multiple physician specialties, as well as dedicated staff in nursing, social work, psychology, pharmacy, nutrition, child life and physical therapy. Patients have easy access to physician consultations within the hospital's subspecialties, including cardiology, nephrology, infectious disease and surgery.

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FIGURE 3. Stepwise Approach for the Classification of Anemia

1. **Determine presence** of anemia based on age-based norms
2. **Use MCV** to classify type of anemia (i.e., macrocytic, microcytic, normocytic)
3. **Obtain reticulocyte count** in ALL patients being evaluated for suspected anemia to determine bone marrow's response to anemia
4. **Evaluate other cell lines** (i.e., platelets, WBC with differential-neutropenia, lymphopenia)
5. **Direct workup** accordingly based on above information