

Evaluation of Anemia in Children

JENNIFER JANUS, MD, *Johns Hopkins Community Physicians, Hagerstown, Maryland*

SARAH K. MOERSCHEL, MD, *West Virginia University Robert C. Byrd Health Sciences Center Eastern Division, Harpers Ferry, West Virginia*

Anemia is defined as a hemoglobin level of less than the 5th percentile for age. Causes vary by age. Most children with anemia are asymptomatic, and the condition is detected on screening laboratory evaluation. Screening is recommended only for high-risk children. Anemia is classified as microcytic, normocytic, or macrocytic, based on the mean corpuscular volume. Mild microcytic anemia may be treated presumptively with oral iron therapy in children six to 36 months of age who have risk factors for iron deficiency anemia. If the anemia is severe or is unresponsive to iron therapy, the patient should be evaluated for gastrointestinal blood loss. Other tests used in the evaluation of microcytic anemia include serum iron studies, lead levels, and hemoglobin electrophoresis. Normocytic anemia may be caused by chronic disease, hemolysis, or bone marrow disorders. Workup of normocytic anemia is based on bone marrow function as determined by the reticulocyte count. If the reticulocyte count is elevated, the patient should be evaluated for blood loss or hemolysis. A low reticulocyte count suggests aplasia or a bone marrow disorder. Common tests used in the evaluation of macrocytic anemias include vitamin B₁₂ and folate levels, and thyroid function testing. A peripheral smear can provide additional information in patients with anemia of any morphology. (*Am Fam Physician*. 2010;81(12):1462-1471. Copyright © 2010 American Academy of Family Physicians.)

An estimated 20 percent of American children will have anemia at some point in their childhood.¹ Anemia is defined as a hemoglobin (Hgb) concentration or red blood cell (RBC) mass less than the 5th percentile for age. Hgb levels vary by age, and many laboratories use adult norms as references; therefore, the patient's Hgb level must be compared with age-based norms to diagnose anemia² (*Table 1*³).

Anemia is usually classified based on the size of RBCs, as measured by the mean corpuscular volume (MCV). Anemia can be microcytic (MCV typically less than 80 μm^3 [80 fL]), normocytic (80 to 100 μm^3 [80 to 100 fL]), or macrocytic (greater than 100 μm^3 [100 fL]). The RBC distribution width is a measure of the size variance of RBCs. A low RBC distribution width suggests uniform cell size, whereas an elevated width (greater than 14 percent) indicates RBCs of multiple sizes.

Etiology

Although some studies have suggested a decline in the prevalence of anemia,^{4,5} the most recent Pediatric Nutrition Surveillance System Report showed an increase among low-income children, from 13 percent in 2002 to 15 percent in 2007.⁶ The causes of anemia vary by age (*Table 2*).^{2,7} Anemia should not

be considered a diagnosis, but a finding that warrants further investigation.⁸ In children, it is usually caused by decreased RBC production or increased RBC turnover.²

Iron deficiency commonly causes decreased RBC production. Risk factors include prematurity, poor diet, consumption of more than 24 oz of cow's milk per day, and chronic blood loss.⁹ Other causes of decreased RBC production include inflammation from chronic infection or other inflammatory conditions, renal failure, medication use, viral illnesses, and bone marrow disorders (*Table 3*).^{2,10}

Increased RBC turnover may be a result of blood loss, mechanical destruction of RBCs, or hemolysis. Hemolysis may result from inherited defects in RBCs; therefore, sex, ethnicity, and family history are potential risk factors. Medications may cause anemia because of immune-mediated hemolysis or oxidative stress. Mechanical destruction may occur in persons with mechanical valves or splenomegaly. RBC loss may also be a result of acute bleeding.²

Diagnosis

CLINICAL DIAGNOSIS

Most children with mild anemia have no signs or symptoms. Some may present with irritability or pica (in iron deficiency), jaundice (in

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Screening for anemia in high-risk infants and toddlers is recommended; universal screening is not.	B	9, 18, 19
If anemia is consistent with iron deficiency in a child six to 36 months of age with low mean corpuscular volume and elevated red blood cell distribution width, it is reasonable to try oral iron therapy for one month before additional diagnostic testing.	C	9, 18, 23
Iron deficiency anemia should be treated with oral iron therapy.	C	9, 18
Iron deficiency (with or without anemia) is associated with negative behavioral and cognitive effects that may not be reversible.	C	28-33
To prevent iron deficiency anemia, adequate dietary iron intake should be ensured in infants older than six months, and cow's milk should be limited to 16 to 24 oz per day in children older than 12 months.	C	9, 22

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

hemolysis), shortness of breath, or palpitations. Physical examination may show jaundice, tachypnea, tachycardia, and heart failure, especially in children with severe or acute anemia.

Pallor has poor sensitivity for predicting mild anemia, but correlates well with severe anemia.¹¹⁻¹³ One study showed that physical examination findings of pallor of the conjunctivae, tongue, palm, or nail beds is 93 percent sensitive and 57 percent specific for the diagnosis of anemia in patients with an Hgb level of less than 5 g per dL (50 g per L).¹⁴ The sensitivity decreases to 66 percent when the Hgb level is 5 to 8 g per dL (50 to 80 g per L).¹⁴ Chronic anemia may be associated with glossitis, a flow murmur, and growth delay, although these conditions are rare in developed countries.¹

DIAGNOSTIC TESTS

Laboratory tests used in the diagnosis of anemia include measurement of ferritin, which reflects iron stores, and transferrin or total iron-binding capacity, which indicates the body's ability to transport iron for use in RBC production.

Hgb measurement fails to detect many cases of early or mild iron deficiency because the life span of RBCs reflect bone marrow iron content from up to 120 days previously. Because reticulocytes survive in the periphery for only one or two days, reticulocyte hemoglobin content (RHC) is a more accurate "real-time" measurement of bone marrow iron status.¹⁵ Alternatively, many cases of anemia in children are not caused by iron deficiency. Therefore, measurement of a single Hgb level may result in unnecessary treatment and

retesting.¹⁶ Measurement of RHC may help avoid this issue. In a study of infants nine to 12 months of age, an Hgb level of less than 11 g per dL (110 g per L) was only 26 percent sensitive in detecting iron deficiency (as measured by a transferrin saturation of less than 10 percent), whereas an RHC of less than 27.5 pg was 83 percent sensitive in detecting iron deficiency.¹⁷ RHC is not available in all laboratories, and more studies are needed to

Table 1. Age-Specific Normative Red Blood Cell Values

Age	Hemoglobin (g per dL)		Hematocrit (%)		Mean corpuscular volume (fL)	
	Mean	2 SDs below mean	Mean	2 SDs below mean	Mean	2 SDs below mean
		Mean		Mean		Mean
26 to 30 weeks' gestation	13.4	11.0	41.5	34.9	118.2	106.7
28 weeks' gestation	14.5	NA	45	NA	120	NA
32 weeks' gestation	15.0	NA	47	NA	118	NA
Full term (cord sample)	16.5	13.5	51	42	108	98
1 to 3 days	18.5	14.5	56	45	108	95
2 weeks	16.6	13.4	53	41	105	88
1 month	13.9	10.7	44	33	101	91
2 months	11.2	9.4	35	28	95	84
6 months	12.6	11.1	36	31	76	68
6 months to 2 years	12.0	10.5	36	33	78	70
2 to 6 years	12.5	11.5	37	34	81	75
6 to 12 years	13.5	11.5	40	35	86	77
12 to 18 years (male)	14.5	13.0	43	36	88	78
12 to 18 years (female)	14.0	12.0	41	37	90	78
Adult (male)	15.5	13.5	47	41	90	80
Adult (female)	14.0	12.0	41	36	90	80

NA = not available; SD = standard deviation.

Adapted with permission from Robertson J, Shilkofski N, eds. *The Harriet Lane Handbook*. 17th ed. Philadelphia, Pa.: Mosby; 2005:337.

Table 2. Age-Specific Causes of Anemia

<i>Cause</i>	<i>Etiology and epidemiology</i>	<i>Presentation</i>	<i>Indices and other laboratory testing</i>
Neonatal¹			
Blood loss	Hemorrhage (placental abruption, subgaleal, traumatic); maternal-fetal and twin-twin transfusion Accounts for 5 to 10 percent of all cases of severe neonatal anemia	Tachypnea, pallor, and mental status change (irritability, poor feeding); >20 percent loss of blood volume results in shock and cardiopulmonary collapse	Anemia with normal indices; reticulocyte count is initially normal, then increases; positive Kleihauer-Betke test in maternal-fetal hemorrhage
Isoimmunization	ABO incompatibility, Rh incompatibility Rh incompatibility occurs in 10.6 per 10,000 live births; 50 percent of these infants develop anemia	Jaundice and mild anemia; infants with severe isoimmunization (e.g., untreated Rh incompatibility) may present with hydrops fetalis	Positive Coombs test; elevated bilirubin level; normocytic anemia with elevated reticulocyte count
Congenital hemolytic anemia	Spherocytosis, G6PD deficiency	Hyperbilirubinemia and moderate jaundice	Low enzyme activity; with hemolysis, smear may show poikilocytosis, reticulocytosis, Heinz bodies, and bite cells (in G6PD deficiency) or spur cells (in pyruvate kinase deficiency)
Congenital infection	Parvovirus B19, human immunodeficiency virus, syphilis, rubella, sepsis	Pallor, irritability, and other findings associated with infection (e.g., deafness)	Normocytic anemia with low reticulocyte count
Diamond-Blackfan syndrome	Congenital pure red cell aplasia resulting from increased apoptosis in erythroid precursors Affects 7 per 1 million live births	Neonatal pallor progressing to symptomatic anemia; average age of diagnosis is 3 months; about 30 percent have other abnormalities	Macrocytic anemia with low reticulocyte count
Fanconi anemia	Increased susceptibility of progenitor cells in bone marrow leads to increased apoptosis, progressing to pancytopenia	Average age of diagnosis is 8 years, but associated congenital abnormalities may facilitate early diagnosis (e.g., café-au-lait spots; microsomey; low birth weight; thumb, renal, skeletal, and eye abnormalities)	Microcytic anemia and reticulocytopenia, thrombocytopenia, or leukopenia; DNA sequencing can detect genetic mutations for Fanconi anemia complementation groups
Infancy to toddlerhood²			
Iron deficiency	Inadequate dietary intake, chronic occult blood loss (excessive cow's milk consumption, inflammatory bowel disease, Meckel diverticulum, parasites) Prevalence is 8 to 15 percent	Usually asymptomatic; severe cases can present with fatigue, pallor, or dyspnea; rarely occurs before 6 months of age; highest risk is at 6 to 36 months of age	Microcytic anemia with elevated RBC distribution width; peripheral smear shows hypochromic microcytes and may show target cells; iron and ferritin levels and iron saturation are low; transferrin level is elevated
Concurrent infection	Bacterial or viral infection leading to cytokine-mediated decrease in iron utilization and RBC production	Presenting symptoms usually result from infectious process	Normocytic or mildly microcytic, low/normal serum iron level with low transferrin level; ferritin level may be elevated because it is an acute phase reactant
Blood loss	Trauma, gastrointestinal bleeding	Tachypnea, tachycardia, pallor, hypotension	Hgb levels may initially be normal, followed by anemia with normal indices
Disorder of Hgb structure or synthesis	Thalassemia, sickle cell disease	Anemia in thalassemia may range from mild and asymptomatic to severe, depending on number of heme chains affected; sickle cell disease presents with hemolysis, pain crises, dactylitis, and aplastic crisis; symptoms are rarely present at birth but typically develop in the first year	Microcytic anemia, low RBC distribution width, and low Mentzer index in thalassemia; Hgb electrophoresis may show Hgb F; smear with basophilic stippling; hemolysis, reticulocytosis, and Hgb S on electrophoresis in sickle cell disease
RBC enzyme defects	G6PD deficiency, pyruvate kinase deficiency 10 percent of the black population has G6PD deficiency	Neonatal hyperbilirubinemia and hemolytic anemia when exposed to oxidative stress	Low enzyme activity; with hemolysis smear may show poikilocytosis, reticulocytosis, Heinz bodies, and bite cells (in G6PD deficiency) or spur cells (in pyruvate kinase deficiency)

continued

Table 2. Age-Specific Causes of Anemia (continued)

Cause	Etiology and epidemiology	Presentation	Indices and other laboratory testing
Infancy to toddlerhood² (continued)			
RBC membrane defects	Spherocytosis, elliptocytosis	Hyperbilirubinemia, splenomegaly, gall bladder disease, and aplastic crisis; autosomal dominant, so family history is positive in about 75 percent of patients	Macrocytosis, reticulocytosis, elevated bilirubin and lactate dehydrogenase levels; spherocytes or elliptocytes on smear; osmotic fragility test is commonly done but not specific
Acquired hemolytic anemias	Antibody-mediated hemolysis, drug-induced hemolysis, hemolytic uremic syndrome, disseminated intravascular coagulation	Jaundice, fatigue, dyspnea	Positive Coombs test and spherocytes visible on smear in antibody-mediated hemolysis; schistocytes visible on smear in hemolytic uremic syndrome or disseminated intravascular coagulation
Transient erythroblastopenia of childhood	Transient immune reaction against erythroid progenitor cells	Anemia after toxin ingestion or viral illness, usually in children 6 months to 3 years of age	Normocytic anemia, initially with reticulocyte count of 0; anemia resolves within 2 months
Leukemia, myelofibrosis	Usually spontaneous, but rates are increased in patients with prior radiation exposure or chemotherapy	Anemia causes pallor, fatigue, and dyspnea; patients with leukemia may present with petechiae, low-grade fever, nonspecific bone pain, gum swelling, or rash	Normocytic anemia with decreased reticulocyte count; leukopenia, leukocytosis, or thrombocytopenia; peripheral smear shows blast cells
Lead poisoning	Risk factors include young age, living in a home built before 1970 or in areas where soil is contaminated, and pica (as in iron deficiency)	In addition to anemia, patients may present with abdominal pain, altered mental status, renal disease, and hypertension	Microcytic anemia may be concurrent with iron deficiency; peripheral smear may show basophilic stippling; hemolysis may be present
Late childhood and adolescence²			
Iron deficiency	Second peak in iron deficiency occurs in adolescence because of growth spurt, menstruation, and poor dietary iron intake	Pallor, fatigue, dyspnea	Same as for infants and toddlers, above
Chronic disease	Renal disease, liver disease, hypothyroidism, other chronic illnesses	Usually mild and asymptomatic	Normocytic or mildly microcytic, low/normal serum iron level with low transferrin level; ferritin level may be elevated because it is an acute phase reactant
Blood loss	Same as for infants and toddlers, above Menstruation in adolescent girls		
Disorders of Hgb synthesis or RBC membrane defects	Same as for infants and toddlers, above		
Acquired hemolytic anemias	Same as for infants and toddlers, above		
Leukemia and other bone marrow disorders	Same as for infants and toddlers, above		

NOTE: Causes listed in decreasing order of approximate prevalence.

G6PD = glucose-6-phosphate dehydrogenase; Hgb = hemoglobin; RBC = red blood cell.

Information from references 2 and 7.

determine whether screening with this test is clinically useful and cost-effective.

Approach to the Child with Anemia: Illustrated Case Studies

ANEMIA IN A NEWBORN

A full-term infant is delivered with the use of forceps; the pregnancy and delivery were otherwise uncomplicated. The

initial examination is normal, but on the second hospital day, he is pale and fussy. The reticulocyte count and bilirubin level are normal, and the Hgb level is 9 g per dL (90 g per L). Repeat physical examination reveals an increased head circumference.

Causes of anemia in the newborn are blood loss, decreased RBC production, and increased RBC turnover. Blood loss during delivery can result from a ruptured

Table 3. Risk Factors for Anemia

<i>Etiology</i>	<i>Risk factor</i>	<i>Comment</i>
Decreased RBC production	Chronic disease	Renal disease can result in anemia because of decreased erythropoietin levels; hypothyroidism can result in macrocytic anemia because of impaired RBC production; chronic inflammation (as in chronic infection or rheumatologic disease) can lead to cytokine-mediated suppression of erythropoiesis; inflammatory bowel disease or celiac disease can result in anemia because of inflammation and nutrient malabsorption
	Iron deficiency ¹⁰	Pica induced by iron deficiency increases risk of lead ingestion, and lead is absorbed more readily in the presence of iron deficiency; iron levels should be tested in patients with lead poisoning
	Poor diet	Inadequate nutrient intake can cause deficiencies in iron, folate, and vitamins A, B ₁₂ , and D
	Prematurity	Decreased iron stores and increased demand for catch-up growth can cause iron deficiency; rarely occurs before birth weight is doubled
Increased RBC turnover	Drug use	Primaquine, sulfamethoxazole, and nitrofurantoin (Furadantin) can lead to hemolysis; this is more pronounced in patients with G6PD deficiency but can occur in any patient; phenytoin (Dilantin) can cause megaloblastic anemia
	Ethnicity	African ancestry in sickle cell disease; Mediterranean, Asian, or African ancestry in thalassemia; Sephardic Jewish, Filipino, Greek, Sardinian, or Kurdish ancestry in G6PD deficiency
	Family history	Thalassemia, spherocytosis, and sickle cell disease; family history may include gallstones and jaundice in addition to anemia
	Mechanical heart valves	Mechanical destruction by the valve can cause hemolysis
	Sex	G6PD deficiency and pyruvate kinase deficiency are X-linked and therefore more common in males
	Splenomegaly	Sequestration and increased destruction of RBCs can cause hemolysis
Both	Infection	Infection can precipitate immune-mediated hemolytic anemia or cause hemolytic crises in patients with inherited enzyme defects and sickle cell disease; can cause RBC aplasia (as in parvovirus B19 infection) or result in transient erythroblastopenia of childhood

G6PD = glucose-6-phosphate dehydrogenase; RBC = red blood cell.

Information from references 2 and 10.

umbilical cord, placenta previa, and abruptio placentae. Maternal-fetal transfusion occurs in 50 percent of all pregnancies, but usually does not cause significant loss of blood volume.⁷ The patient's history eliminates most of these causes.

A normal reticulocyte count confirms that the infant's bone marrow is functional. This rules out causes of decreased RBC production, including Fanconi anemia, Diamond-Blackfan syndrome, and congenital infections.

Cranial hemorrhages are often associated with birth trauma, including vacuum and forceps delivery. In particular, subgaleal bleeds can be of sufficient volume to cause shock. Physical examination findings may include mental status changes, jaundice, tachycardia or tachypnea, and increased head circumference.⁷

In this patient, a computed tomography scan confirms a subgaleal hemorrhage, and the infant is transferred to a neonatal intensive care unit for transfusion and monitoring.

In newborns, an elevated bilirubin level in association with anemia suggests hemolysis. If this infant's bilirubin level had been elevated, further testing would have included a Coombs test to evaluate for isoimmunization (as in ABO or Rh incompatibility) and a peripheral smear

to evaluate for spherocytosis or other RBC membrane defects. Testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency should be considered if the patient's ethnicity or family history is a risk factor.

MICROCYTIC ANEMIA IN AN INFANT

A 12-month-old boy of Mediterranean descent presents for a health maintenance examination. He consumes 32 oz of whole milk daily. The medical history and review of systems are normal. On physical examination, the patient is found to have an elevated weight for length. No other abnormalities are noted. Laboratory testing shows that the patient's Hgb level is 9.8 g per dL (98 g per L). The MCV is low (70 μm^3 [70 fL]), and the RBC distribution width is elevated (18 percent). The RBC count is 5.0×10^6 per mm^3 (5.0×10^{12} per L). The child is presumptively treated with oral iron therapy, and after one month, the Hgb level is 11.2 g per dL (112 g per L). After another month of iron therapy, the Hgb level has normalized at 13 g per dL (130 g per L).

Neither the Centers for Disease Control and Prevention, the American Academy of Pediatrics, nor the U.S. Preventive Services Task Force recommends universal screening for anemia. Instead, children at risk should be identified and then undergo evaluation between nine and 12 months of age (Table 4).^{9,18,19} This child's excessive

Table 4. Comparison of Recommendations for Screening for Anemia

Organization	Recommendations	High-risk groups
American Academy of Pediatrics	Screening is recommended at 9 to 12 months of age and again 6 months later for all infants in populations with high rates of iron deficiency, or (in populations with a rate of 5 percent or less) in infants with medical risks or whose diet puts them at risk of iron deficiency	Premature infants Low-birth-weight infants Infants fed low-iron formula Breastfed infants older than 6 months who are not receiving iron supplementation
Centers for Disease Control and Prevention	Screening is recommended for children from low-income or newly immigrated families between 9 and 12 months of age, then 6 months later, then annually from 2 to 5 years of age Screening should be considered for preterm and low-birth-weight infants before 6 months of age if they are not fed iron-fortified formula Infants and young children with risk factors should be assessed at 9 to 12 months of age, and again 6 months later Beginning in adolescence, all nonpregnant women should be screened every 5 to 10 years	Infants fed non-iron-fortified formula or cow's milk before 12 months of age Breastfed infants older than 6 months without adequate iron supplementation Children who consume more than 24 oz of cow's milk per day Children with special health care needs (e.g., medications that interfere with iron absorption, chronic infection, inflammatory disorders, blood loss)
U.S. Preventive Services Task Force	No recommendation for or against screening for iron deficiency anemia in asymptomatic children 6 to 12 months of age Screening at 9 to 12 months of age is recommended for high-risk infants	Premature infants Low-birth-weight infants Recent immigrants Adolescent girls who follow fad diets or who are obese Adult females

Information from references 9, 18, and 19.

milk consumption and weight are risk factors for anemia²⁰⁻²²; therefore, evaluation is justified.

Iron deficiency is characterized by microcytosis with an elevated RBC distribution width. Because the anemia is mild and the history and laboratory values are consistent with iron deficiency, it is appropriate to treat presumptively with oral iron therapy and repeat testing in one month²³ (Figure 1). Treatment for mild anemia is 3 to 6 mg of elemental iron per kg per day.²⁴ Once-daily dosing results in similar improvement as two- or three-times-daily dosing and does not significantly increase adverse effects.²⁵

An Hgb increase of more than 1 g per dL (10 g per L) after iron therapy has been started confirms the diagnosis of iron deficiency. If the Hgb level does not increase or if the initial anemia is severe, further evaluation should include a complete blood count (CBC), peripheral blood smear, iron studies, and fecal occult blood testing. Lead testing should also be considered.

Patients with thalassemia typically have a Mentzer index of less than 13 (Table 5)^{26,27} and may be of African, Asian, or Mediterranean descent. In patients with thalassemia, Hgb electrophoresis may show an increase in levels of Hgb A or F.

Sideroblastic anemia, which is rare, results in a high RBC distribution width with normal or elevated iron levels; diagnosis requires bone marrow aspiration. Iron is utilized by tissues other than bone marrow, including the brain. Studies show an association between

iron deficiency and impaired neurocognitive performance.²⁸⁻³³ The association is not definitively causal, and studies do not show an immediate improvement in psychomotor development or cognitive performance after treatment has commenced. However, long-term studies are few and conflicting.³⁴ Until further studies provide clarity, iron deficiency should be treated until one month after normalization of Hgb levels. The total treatment course is typically three months. If a longer course is needed, further investigation should include a CBC, peripheral blood smear, iron studies, and fecal occult blood testing.²³

NORMOCYTIC ANEMIA IN AN OLDER CHILD

A previously healthy eight-year-old boy of Filipino descent presents with increasing fatigue for the past five days. He has low-grade fever and nonspecific musculoskeletal pain. He has had no symptoms of upper respiratory infection. Physical examination shows pallor, pale conjunctivae, scattered facial petechiae, tachycardia, and a flow murmur. There is no scleral icterus. A CBC shows an Hgb level of 7.8 g per dL (78 g per L) and an MCV of 90 μm^3 (90 fL). The white blood cell count is 14,000 per mm^3 (14.00×10^9 per L), and the platelet count is 368×10^3 per mm^3 (368×10^9 per L). The reticulocyte count is 0.21 percent (normal range in an eight-year-old is 0.5 to 1.0 percent). The peripheral smear shows 21 percent lymphoblasts.

This is normocytic anemia in a previously healthy child. Although normocytic anemia commonly results

Evaluation of Low Hemoglobin Levels

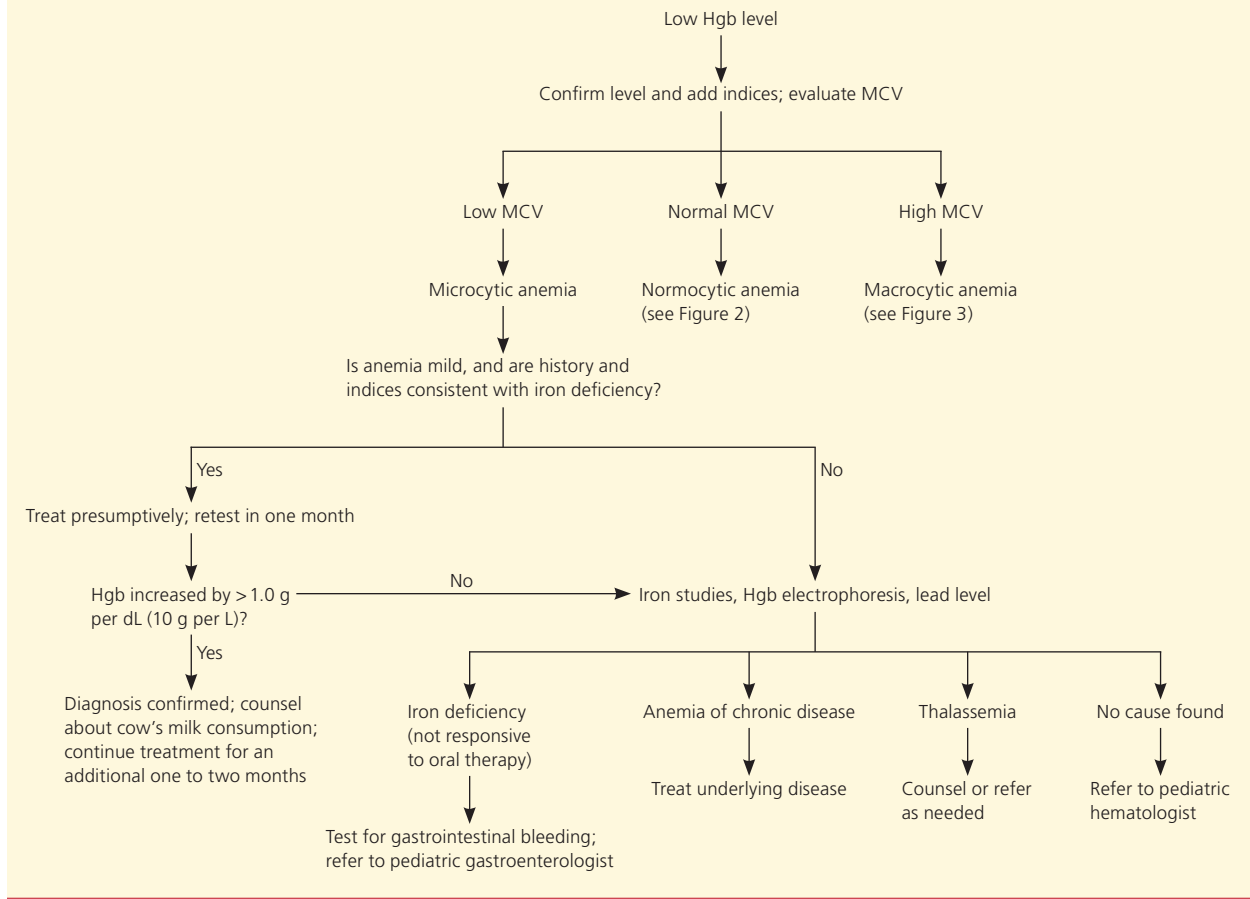


Figure 1. Algorithm for evaluation of low hemoglobin (Hgb) levels in children. (MCV = mean corpuscular volume.)

from early iron deficiency or chronic disease, this patient has findings suggesting an acute process (pallor, tachycardia, and flow murmur). Hemoglobinopathies, enzyme defects, RBC membrane defects, and other hemolytic anemias result in normocytic anemia. Given his sex and ethnicity, G6PD deficiency is in the differential diagnosis. However, he has no history and is not jaundiced, which makes hemolysis unlikely.

In a child who otherwise appears well and has had a recent viral infection, transient erythroblastopenia of childhood (TEC) should be considered. This condition usually occurs in children six months to three years of age after a viral infection or exposure to toxic agents. It

Table 5. Calculation of the Mentzer Index

Example patient	MCV (fL)	RBC count ($\times 10^6$ per mm^3)	Mentzer index (MCV/RBC count)	Comments
5-year-old black child with pallor	64	5.3	12	Mentzer index < 13 suggests thalassemia
2-year-old child who drinks 30 oz of cow's milk daily	72	4.8	15	Mentzer index > 13 suggests iron deficiency

NOTE: Although commonly used, the Mentzer index and other indices used to differentiate iron deficiency from thalassemia are not uniformly reliable.²⁶

MCV = mean corpuscular volume; RBC = red blood cell.

Information from references 26 and 27.

Evaluation of Normocytic Anemia

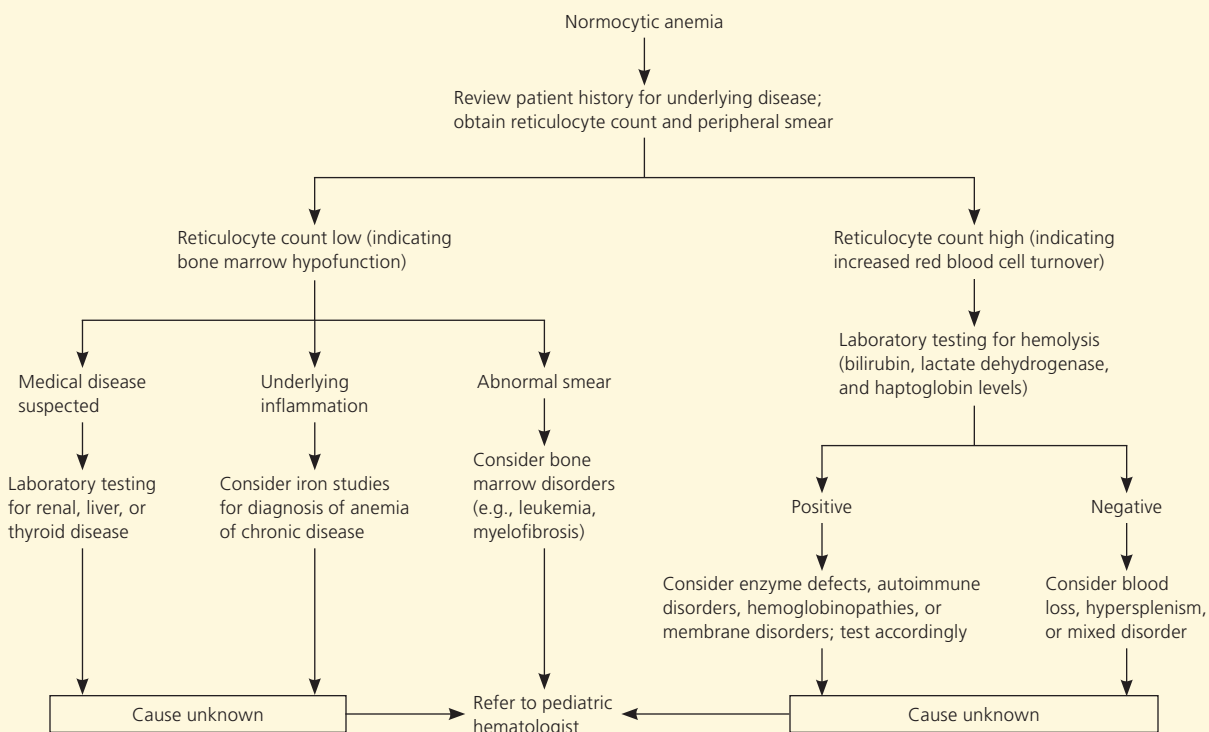


Figure 2. Algorithm for evaluation of normocytic anemia in children.

is the result of an immune reaction against erythroid progenitor cells. In patients with TEC, the initial reticulocyte count is zero, but slowly increases as the patient recovers, which typically occurs within two months of onset.³⁵ This child's age, ill appearance, and lack of viral symptoms make TEC less likely.

The first step in evaluation of normocytic anemia is determination of the reticulocyte count (*Figure 2*) to distinguish cases of increased RBC turnover, such as hemolysis, from bone marrow disorders. The low reticulocyte count suggests bone marrow hypofunction. Leukemia and aplastic anemia reduce RBC production. Because leukemia is a consideration in the differential diagnosis for this patient, a peripheral smear is ordered, which confirms the diagnosis of leukemia.

If the diagnosis had been less clear, further evaluation would have included a careful history and testing of iron levels and liver, kidney, and thyroid function to assess for chronic disease. Low iron saturation suggests early iron deficiency. Normal or elevated iron saturation in the presence of low serum iron levels suggests infection or chronic disease.

Other Considerations

Macrocytic anemia is rare in children. The initial workup is a peripheral smear (*Figure 3*).³⁶ The presence of hypersegmented neutrophils signals a megaloblastic anemia,

which is caused by folate or vitamin B₁₂ deficiency or other disorders of DNA synthesis. Nonmegaloblastic causes of macrocytosis include alcoholism, hemolysis, hemorrhage, hepatic disease, bone marrow disorders (e.g., aplastic anemia, myelodysplasia, sideroblastic anemia), and hypothyroidism. Subsequent testing is based on peripheral smear findings.³⁶

Older children and adolescents are also at risk of anemia. The combination of a growth spurt and the onset of menstruation leaves adolescent girls at particularly high risk of iron deficiency anemia.

Treatment and Prevention

Iron deficiency is treated orally; otherwise, treatment is geared toward the underlying cause of anemia. Symptomatic patients and those with severe anemia should receive a blood transfusion while evaluation for the underlying cause is undertaken. Transfusion is typically given at a volume of 10 mL per kg, infused at a rate of no more than 5 mL per kg per hour. The patient should be monitored for signs of heart failure during transfusion.

The U.S. Food and Drug Administration recommends adequate iron intake to prevent iron deficiency anemia (*Table 6*⁹). One half of American toddlers do not receive the recommended daily intake of iron.³⁷ However, it is not clear whether iron supplementation reduces the incidence of anemia. Studies in countries outside the United

Evaluation of Macrocytic Anemia

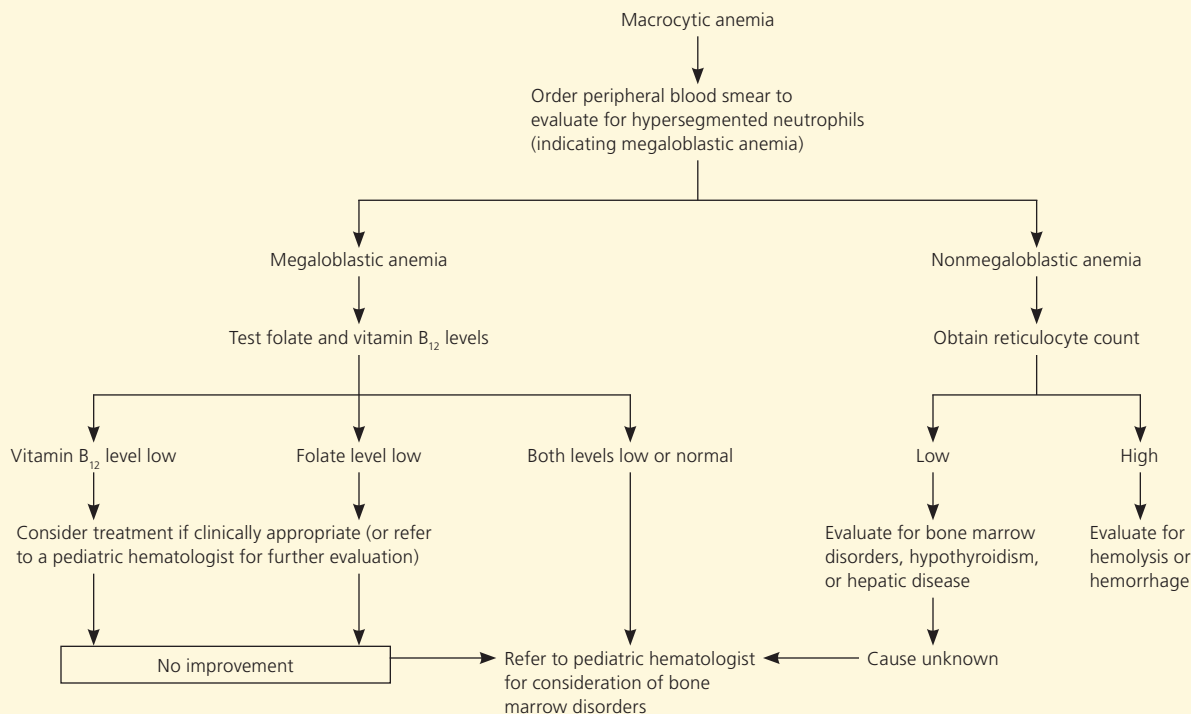


Figure 3. Algorithm for evaluation of macrocytic anemia in children.

Adapted with permission from Janus J, Moerschel SK. Evaluation of anemia in children. *Am Fam Physician.* 2010;81(12):1470.

States have had promising results. However, a randomized study in the United States demonstrated that high-risk, six-month-old infants who received 10 mg of supplemental iron per day did not have a reduced incidence of anemia or abnormal indices indicative of iron deficiency.³⁸

In the first four to six months of life, full-term infants use hepatic stores of iron in addition to dietary iron in formula or breast milk; iron supplementation is not required in these children. Preterm infants do not have adequate hepatic iron stores and require larger amounts of iron for catch-up growth. These infants should receive supplemental iron. Starting at four to six months of age, infants require an additional source of iron.³⁹ One half cup of iron-fortified cereal contains 90 percent of the recommended daily intake of iron for a six- to 12-month-old infant. Lean meats, beans, iron-fortified whole grains, tofu, and spinach are other iron-rich options for infants who consume solid foods.

Table 6. Daily Iron Requirements for Infants and Young Children

Age	Daily iron requirement	Source
Up to 4 to 6 months (full-term infants)	0.27 mg	Breast milk or iron-fortified formula
4 to 6 months to 1 year (full-term infants)	11 mg	Breast milk or formula plus iron-rich foods*
1 month to 1 year (premature or low-birth-weight infants)	2 to 4 mg per kg	Iron-fortified preterm formula or iron supplementation (2 mg per kg per day) plus breast milk and iron-rich foods
1 to 3 years	7 mg	Iron-rich foods

*—If a full-term breastfed infant cannot consume adequate iron after 6 months of age, supplementation is necessary (1 mg per kg per day).

Information from reference 9.

The Authors

JENNIFER JANUS, MD, FAAP, is an internist and pediatrician with Johns Hopkins Community Physicians, part of the Johns Hopkins Health System, in Hagerstown, Md. At the time this article was written, she was a clinical assistant professor in the Departments of Family Medicine, Internal Medicine, and Pediatrics at the West Virginia University Robert C. Byrd Health Sciences Center Eastern Division, Harpers Ferry.

SARAH K. MOERSCHER, MD, FAAP, is a clinical assistant professor in the Departments of Family Medicine and

Pediatrics at the West Virginia University Robert C. Byrd Health Sciences Center Eastern Division.

Address correspondence to Jennifer Janus, MD, FAAP, 12916 Conamar Dr., Ste. 204, Hagerstown, MD 21742 (e-mail: jcox21@jhmi.edu). Reprints are not available from the authors.

Author disclosure: Nothing to disclose.

REFERENCES

- Irwin JJ, Kirchner JT. Anemia in children. *Am Fam Physician*. 2001;64(8):1379-1386.
- Oski FA, Brugnara C, Nathan DG. A diagnostic approach to the anemic patient. In: *Nathan and Oski's Hematology of Infancy and Childhood*. 6th ed. Philadelphia, Pa.: Saunders; 2003:409-418.
- Robertson J, Shilkofski N, eds. *The Harriet Lane Handbook*. 17th ed. Philadelphia, Pa.: Mosby; 2005:337.
- Cusick SE, Mei Z, Freedman DS, et al. Unexplained decline in the prevalence of anemia among US children and women between 1988-1994 and 1999-2002. *Am J Clin Nutr*. 2008;88(6):1611-1617.
- Oken E, Rifas-Shiman SL, Kleinman KP, Scanlon KS, Rich-Edwards JW. Trends in childhood anemia in a Massachusetts health maintenance organization, 1987-2001. *MedGenMed*. 2006;8(3):58.
- Borland EW, Dalenius K, Grummer-Strawn L, Mackintosh H, Polhamus B, Smith BL. *Pediatric Nutrition Surveillance: 2007 Report*. Atlanta, Ga.: Centers for Disease Control and Prevention; 2009.
- Bizzarro MJ, Colson E, Ehrenkranz RA. Differential diagnosis and management of anemia in the newborn. *Pediatr Clin North Am*. 2004;51(4):1087-1107.
- Olhs RK, Christensen RD. Diseases of the blood. In: Behrman RE, Kliegman R, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia, Pa.: Saunders; 2004:1604-1634.
- Pediatric Nutrition Handbook*. 6th ed. Elk Grove Village, Ill.: American Academy of Pediatrics; 2009:403-422.
- Wright RO, Tsaih SW, Schwartz J, Wright RJ, Hu H. Association between iron deficiency and blood lead level in a longitudinal analysis of children followed in an urban primary care clinic. *J Pediatr*. 2003;142(1):9-14.
- Stoltzfus RJ, Edward-Raj A, Dreyfuss ML, et al. Clinical pallor is useful to detect severe anemia in populations where anemia is prevalent and severe. *J Nutr*. 1999;129(9):1675-1681.
- Montresor A, Albonico M, Khalfan N, et al. Field trial of a haemoglobin colour scale: an effective tool to detect anaemia in preschool children. *Trop Med Int Health*. 2000;5(2):129-133.
- Strobach RS, Anderson SK, Doll DC, Ringenberg QS. The value of the physical examination in the diagnosis of anemia. Correlation of the physical findings and the hemoglobin concentration. *Arch Intern Med*. 1988;148(4):831-832.
- Luby SP, Kazembe PN, Redd SC, et al. Using clinical signs to diagnose anaemia in African children. *Bull World Health Organ*. 1995;73(4):477-482.
- Mast AE, Blinder MA, Lu Q, Flax S, Dietzen DJ. Clinical utility of the reticulocyte hemoglobin content in the diagnosis of iron deficiency. *Blood*. 2002;99(4):1489-1491.
- White KC. Anemia is a poor predictor of iron deficiency among toddlers in the United States: for heme the bell tolls. *Pediatrics*. 2005;115(2):315-320.
- Ullrich C, Wu A, Armsby C, et al. Screening healthy infants for iron deficiency using reticulocyte hemoglobin content. *JAMA*. 2005;294(8):924-930.
- Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR Recomm Rep*. 1998;47(RR-3):1-29.
- U.S. Preventive Services Task Force. Screening for iron deficiency anemia, including iron supplementation for children and pregnant women: recommendation statement. Rockville, Md.: Agency for Healthcare Research and Quality; 2006. AHRQ publication no. 06-0589. <http://www.ahrq.gov/clinic/uspstf/uspstfiron.htm>. Accessed February 18, 2010.
- Brotanek JM, Gosz J, Weitzman M, Flores G. Iron deficiency in early childhood in the United States: risk factors and racial/ethnic disparities. *Pediatrics*. 2007;120(3):568-575.
- Nead KG, Halterman JS, Kaczorowski JM, Auinger P, Weitzman M. Overweight children and adolescents: a risk group for iron deficiency. *Pediatrics*. 2004;114(1):104-108.
- American Academy of Pediatrics Committee on Nutrition. The use of whole cow's milk in infancy. *Pediatrics*. 1992;89(6 pt 1):1105-1109.
- Segel GB, Hirsh MG, Feig SA. Managing anemia in pediatric office practice: part 1. *Pediatr Rev*. 2002;23(3):75-84.
- Lexi-Comp, American Pharmaceutical Association. *Pediatric Dosage Handbook*. 12th ed. Hudson, Ohio: Lexi-Comp; 2005:623-626.
- Zlotkin S, Arthur P, Antwi KY, Yeung G. Randomized, controlled trial of single versus 3-times-daily ferrous sulfate drops for treatment of anemia. *Pediatrics*. 2001;108(3):613-616.
- Mentzer WC Jr. Differentiation of iron deficiency from thalassemia trait. *Lancet*. 1973;1(7808):882.
- Demir A, Yarali N, Fisgin T, Duru F, Kara A. Most reliable indices in differentiation between thalassemia trait and iron deficiency anemia. *Pediatr Int*. 2002;44(6):612-616.
- Walter T, De Andraca I, Chadud P, Perales CG. Iron deficiency anemia: adverse effects on infant psychomotor development. *Pediatrics*. 1989;84(1):7-17.
- Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics*. 2000;105(4):e51.
- Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG. Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. *Pediatrics*. 2001;107(6):1381-1386.
- Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. *J Nutr*. 2001;131(2S-2):649S-666S.
- McCann JC, Ames BN. An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function. *Am J Clin Nutr*. 2007;85(4):931-945.
- Beard JL. Why iron deficiency is important in infant development. *J Nutr*. 2008;138(12):2534-2536.
- Logan S, Martins S, Gilbert R. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia. *Cochrane Database Syst Rev*. 2001;(2):CD001444.
- Walters MC, Abelson HT. Interpretation of the complete blood count. *Pediatr Clin North Am*. 1996;43(3):599-622.
- Davenport J. Macrocytic anemia. *Am Fam Physician*. 1996;53(1):155-162.
- U.S. Department of Agriculture. Supplementary data tables: USDA's 1994-1996 continuing survey of food intakes by individuals. <http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/Supp.pdf>. Accessed September 3, 2008.
- Geltman PL, Meyers AF, Mehta SD, et al. Daily multivitamins with iron to prevent anemia in high-risk infants: a randomized clinical trial. *Pediatrics*. 2004;114(1):86-93.
- Chaparro CM. Setting the stage for child health and development: prevention of iron deficiency in early infancy. *J Nutr*. 2008;138(12):2529-2533.