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**Microcytic Anemia**  
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# Microcytic Anemia

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to this article.

**Objectives** After completing this article, readers should be able to:

1. Discuss the common causes of microcytic anemia in children.
2. Define the most common cause of microcytic anemia in children.
3. Distinguish iron deficiency anemia from beta thalassemia trait.
4. Recognize when disorders of beta-globin may present in infants.

## Microcytic Anemia

Anemia is the most common hematologic abnormality that pediatricians encounter. The differential diagnosis for anemia in children includes congenital, acquired, benign, malignant, common, and extraordinarily rare disorders. Thankfully, most conditions cause consistent changes in the mean cell volume (MCV) of red blood cells (RBCs) and can be grouped by using this parameter. In children, anemia is caused most often by disorders that result in smaller-than-normal RBCs (microcytosis) (Table 1). With a thorough history, a good physical examination, and perhaps some additional blood work, the correct cause of a child's microcytic anemia can be discovered.

## Is It Anemia? Is It Microcytic?

Automated blood counters may not take into account the normal variations in hemoglobin/hematocrit and MCV that are seen throughout childhood. Results reported as abnormal must be compared with age-specific values (Table 2). Values that are 2 standard deviations below the age-appropriate mean can be considered abnormal.

## Hemoglobin Overview

Because disorders of heme metabolism or globin synthesis can lead to microcytic anemia, an appreciation of hemoglobin structure and how it changes over the first few months after birth is important. Hemoglobin is produced by a multistep process involving several enzymes in mitochondria and the cytosol. Hemoglobin consists of an iron-containing heme ring associated with four globin chains (Fig. 1). Except for the first few weeks after conception, the dominant hemoglobin in utero is fetal hemoglobin (HbF), composed of the heme ring associated with two alpha-globin chains and two gamma-globin chains. As pregnancy continues, the fetus transitions to an adult hemoglobin pattern, gradually decreasing the amount of HbF and increasing the amounts of hemoglobin A (HbA) (heme ring associated with two alpha-chains and two beta-chains [ $\alpha_2\beta_2$ ]) and A2 (HbA2) (heme ring with two alpha-chains and two delta-chains). At birth, HbF accounts for approximately 80% of hemoglobin and HbA for 20%. Between 6 and 10 months after birth, most children have a distribution of hemoglobin types similar to that of adults. Thus, disorders of beta-globin genes, such as beta thalassemia or sickle cell disease, may not become apparent until partway through the first postnatal year.

## History and Physical Examination

Key aspects of the history and physical examination always should be addressed when evaluating a child who has microcytic anemia.

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**Table 1. Causes of Microcytic Anemia**

**Common**

- Iron deficiency
- Thalassemia trait (alpha or beta)

**Less Common**

- Hemoglobinopathy (with or without thalassemia)
- Inflammation
- Thalassemia major
- Lead toxicity
- Sideroblastic anemia

**Signs, Symptoms, History**

Many children who have microcytic anemia have no complaints. The disorder frequently is detected as part of an office screening program or when a blood count is obtained for another illness. When evaluating a child who has microcytic anemia, the results of the newborn screen for hemoglobin disorders should be reviewed. Gestational age at time of birth should be determined because infants born preterm are at higher risk for iron deficiency than are term infants. Older children may become noticeably tired. Significant iron deficiency can cause irritability. Family members, often those who see the child only intermittently, sometimes note pallor. Pallor can be appreciated in the conjunctiva, gums, and

creases of the palms; in darker-pigmented patients, looking for pallor in the nailbeds is particularly helpful.

The physical examination may show tachycardia at rest and a flow murmur. The presence of splenomegaly should raise the question of a hemoglobinopathy or thalassemia. Bony deformations such as frontal bossing or maxillary dysplasia suggest bone marrow hypertrophy, as seen in the major thalassemia syndromes.

**Diet**

Because nutritional iron deficiency is the primary cause of microcytic anemia in children, a dietary history is essential. Particular attention should be given to the volume of cow milk consumed and the amount and type of meats and vegetables eaten. Pica may be either a sign or a cause of iron deficiency or lead poisoning. Craving and eating ice (pagophagia) is relatively common with iron deficiency.

**Blood Loss**

Potential signs of blood loss (and, thus, iron loss), such as hematochezia (bright red blood per rectum), melena, and heavy menses, should be investigated.

**Family History**

Some causes of microcytic anemia are inherited. Physicians should ask about a diagnosis of anemia in other family members. Because certain disorders are more common in particular ethnic or racial groups, it is appro-

**Table 2. Hemoglobin and Mean Cell Volume Throughout Childhood\***

Age	Mean Hemoglobin (g/dL) (g/L)	"-2SD"	Mean Hematocrit (%) (Proportion of 1.0)	"-2SD"	Mean Cell Volume (mcm <sup>3</sup> )	"-2SD"
Birth	16.5 (165)	13.5 (135)	51 (0.51)	42 (0.42)	108	98
1 to 3 d	18.5 (185)	14.5 (145)	56 (0.56)	45 (0.45)	108	95
1 mo	14.0 (140)	10.0 (100)	43 (0.43)	31 (0.31)	104	85
2 mo	11.5 (115)	9.0 (90)	35 (0.35)	28 (0.28)	96	77
3 to 6 mo	11.5 (115)	9.5 (95)	35 (0.35)	29 (0.29)	91	74
6 mo to 2 y	12.0 (120)	10.5 (105)	36 (0.36)	33 (0.33)	78	70
2 to 6 y	12.5 (125)	11.5 (115)	37 (0.37)	34 (0.34)	81	75
6 to 12 y	13.5 (135)	11.5 (115)	40 (0.40)	35 (0.35)	86	77
12 to 18 y						
Female	14.0 (140)	12.0 (120)	41 (0.41)	36 (0.36)	90	78
Male	14.5 (145)	13.0 (130)	43 (0.43)	37 (0.37)	88	78
18 to 49 y						
Female	14.0 (140)	12.0 (120)	41 (0.41)	36 (0.36)	90	80
Male	15.5 (155)	13.5 (135)	47 (0.47)	41 (0.41)	90	80

\*Adapted from Nathan DG, Orkin SH, Look AT, Ginsburg D, eds. *Nathan and Oski's Hematology of Infancy and Childhood*. 6th ed. Philadelphia, Pa: Saunders; 2003, with permission from Elsevier.

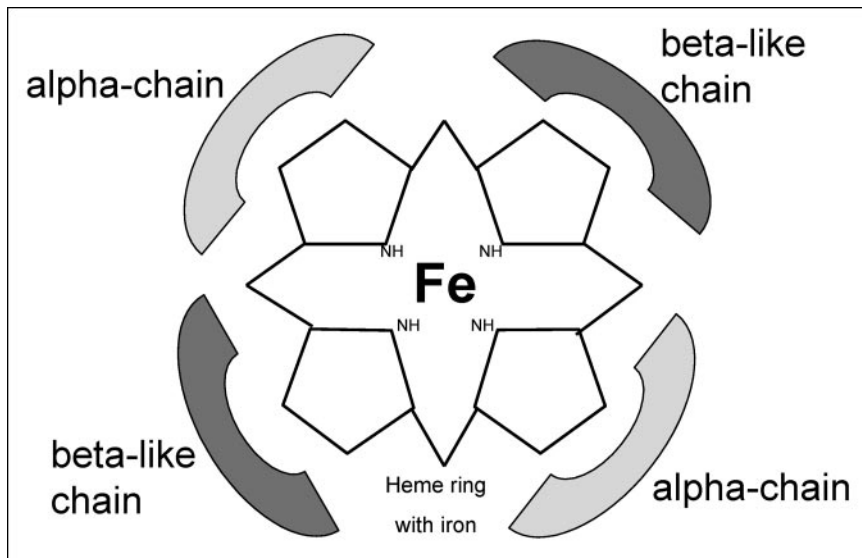


Figure 1. Schematic of hemoglobin structure.

appropriate to ask about the patient's ancestry. Most families are not offended if the physician explains the logic for asking about racial or national background. Sickle hemoglobinopathies are more prevalent in African-Americans and Hispanics; hemoglobin E disorder is seen most often in Southeast Asians. The thalassemias are most common in African-Americans and people whose ancestry is from the Mediterranean region or southeast Asia. A negative report of lineage from these regions/ethnicities/races, however, does not rule out any given disorder.

### Iron Deficiency

Iron is necessary for the production of hemoglobin, myoglobin, and cytochrome enzymes, which are present in all tissues. Iron deficiency, thus, affects all organ systems. Low concentrations of iron, even without anemia, have been associated with poor cognitive achievement, poor school performance, and behavioral problems. Dietary iron is absorbed in the duodenum, but not all sources of iron are absorbed equally well. Heme iron, found in meats and shellfish, is absorbed more readily than is the nonheme iron of beans, grains, and vegetables. Although the concentration of iron in human milk is similar to that of formula, human milk iron is absorbed more readily than formula iron. The presence of acidic food enhances the absorption of dietary iron.

Children become iron deficient from either inadequate dietary intake (the most common cause) or from blood loss, usually gastrointestinal (GI) or, in older females, menstrual bleeding. Infants and children who

consume large amounts of cow milk are particularly prone to iron deficiency. Cow milk iron is poorly absorbed and filling and slows gastric emptying, thus preventing the consumption of heme-containing foods; calcium inhibits iron absorption; and cow milk may cause a protein allergy with GI bleeding (microscopic or gross). Ideally, children should be limited to fewer than 16 oz of cow milk each day. The finding of iron deficiency in a patient who has a normal dietary history should prompt an evaluation for a source of bleeding, such as occult or overt GI bleeding or menorrhagia.

### Laboratory Findings

In addition to microcytosis, iron deficiency results in an increase in the red cell distribution width and decreases in the reticulocyte count, RBC number, and mean cellular hemoglobin. Platelet number may be elevated. For patients who have a history consistent with poor iron intake or blood loss and RBC indices consistent with iron deficiency, no additional laboratory work may be needed. Treatment of the underlying cause of the deficiency can begin, and oral iron replacement can be initiated. An increase in hemoglobin, reticulocyte count, and MCV within 1 to 4 weeks of starting iron therapy is the best test to confirm the diagnosis of iron deficiency.

If the clinical history or laboratory findings are inconclusive or conflicting, more specific measurements of iron status may be warranted. Concentrations of serum ferritin, an indirect measurement of body iron stores, are decreased in iron deficiency. However, as an inflammatory marker, ferritin values can be elevated during acute or chronic illness. Total iron-binding capacity (TIBC) may be elevated, and the transferrin saturation  $\times 100$  (serum iron/TIBC) is low. Concentrations of free erythrocyte protoporphyrin (FEP), a heme precursor, may be elevated, reflecting the body's inability to complete heme production without iron. FEP also may be elevated with lead toxicity.

In the presence of a microcytic anemia, a Mentzer index (MCV/RBC) score above 13 is consistent with iron deficiency, and a value below 13 is consistent with beta thalassemia trait. The index, however, should be used only as a "screen."

## Treatment

Iron deficiency and its underlying cause should be addressed concurrently by decreasing the consumption of cow milk, increasing the amount of heme-rich foods in the diet, or stopping bleeding. For parents who have difficulty limiting their child's milk consumption, it is helpful to point out that humans are the only animals to drink routinely the milk of another species.

Assuming a normal functioning gut, iron should be replaced orally. Intramuscular or intravenous replacement of iron is inappropriate for routine nutritional iron deficiency. The usual dose for oral replacement is 6 mg/kg per day of elemental iron. The dose may be divided either three times (tid) or twice (bid) daily, depending on patient preference or on the development of adverse effects such as nausea, stomach cramping, constipation, or diarrhea. Vitamin C (ascorbic acid) increases the absorption of iron, and supplements ideally are taken with vitamin C-containing foods or juices.

There does not appear to be any discernible difference in the tolerability of different iron formulations. Ferrous sulfate is the least expensive. Patients should return after 1 to 2 weeks of therapy to have an increase in hemoglobin concentration and reticulocyte count documented; these findings assess compliance with the therapy and can

**Iron** replacement should continue for at least 2 months after the anemia has been corrected, assuming that the underlying cause has been addressed.

validate the diagnosis. Children who have severe iron deficiency anemia (eg, hemoglobin <5 to 6 g/dL [50 to 50 g/L]) should return earlier to assure that the anemia is not worsening. Iron replacement should continue for at least 2 months after the anemia has been corrected, assuming that the underlying cause has been addressed.

Some children who are breastfed exclusively may benefit from supplemental iron, especially if they were born preterm, have not started taking iron-fortified cereals, or have been shown by laboratory tests to have low iron stores.

The most common causes of treatment failure are noncompliance and failure to treat the cause of the iron deficiency. Disorders of malabsorption, such as celiac sprue, are rarely the cause for lack of response. Thalassemia

trait, frequently mistaken for iron deficiency, must be considered if there is no response to iron therapy.

## Thalassemias

The thalassemias are a family of disorders that result from decreased globin chain production. Either alpha-globin (alpha thalassemias) or beta-globin (beta thalassemias) production may be decreased. The abnormalities result in *quantitative* changes in globins, as opposed to hemoglobinopathies, in which globin defects are *qualitative* or *functional*.

### Beta Thalassemias

Two genes control beta-globin production, one on each chromosome 11. Depending on the particular mutation, beta-globin production can range from nearly normal to entirely absent.

A one-gene defect results in beta thalassemia trait. This disorder is seen most commonly in African-Americans and people of Mediterranean descent. Children who have beta thalassemia trait are asymptomatic and have no physical findings.

If both beta-globin genes are completely nonfunctional, beta thalassemia major (Cooley anemia) results. No beta-globin is available as the infant transitions from the fetal to adult hemoglobin pattern. Thus, children who have beta thalassemia major present when HbA (alpha<sub>2</sub>beta<sub>2</sub>) is expected to be the dominant hemoglobin, sometime during the second half of the first postnatal year. Physical findings may include hepatosplenomegaly,

poor growth, and in untreated cases, frontal bossing and maxillary hyperplasia resulting from deformation of cortical bone due to bone marrow erythroid hyperplasia.

In beta thalassemia intermedia, there is some degree of beta-globin gene activity between the two genes. The amount of beta-globin produced may be so minimal as to present a clinical picture identical to that of beta thalassemia major or it may be sufficient for transfusions to be avoided. Much depends on how well a patient who has beta thalassemia intermedia tolerates anemia and the physician's threshold for performing transfusions.

**LABORATORY FINDINGS.** Children who have beta thalassemia trait have a microcytic anemia. However, as opposed to iron deficiency, the concentrations of ferritin,

**Table 3. Differences Among Microcytic Anemias**

	Iron Deficiency	Beta Thalassemia Trait	Chronic Inflammation	Lead Toxicity
MCV	Low	Low	Normal–low	Normal–low
RDW	High	Normal	Normal	Normal–high
RBC number	Low	Normal–high	Normal	Low
Mentzer Index (MCV/RBC)	> 13	< 13	N/A	N/A
Platelet count	Normal–high	Normal	Normal–high	Normal
Ferritin	Low	Normal	Normal–high	Normal–low
Transferrin saturation (serum iron/TIBC) × 100	Low	Normal	Low	Normal–low
Hemoglobin electrophoresis	Normal	Increased HbA <sub>2</sub> ; +/- increased HbF	Normal	Normal
Response to iron	Improves	No change	No change	No change
Other			Elevated ESR or CRP	Elevated lead concentration

MCV=mean cell volume, RDW=red cell distribution width, RBC=red blood cell, TIBC=total iron-binding capacity, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, HbA<sub>2</sub>=hemoglobin A<sub>2</sub>, HbF=fetal hemoglobin

serum iron, TIBC, and FEP are normal. The Mentzer index (MCV/RBC) is usually less than 13. Hemoglobin electrophoresis shows essentially normal amounts of HbA and increased amounts of HbA<sub>2</sub> and HbF. Because beta thalassemia trait and iron deficiency are the most common microcytic anemias encountered in children, it is important to distinguish between them (Table 3).

The blood count in beta thalassemia major shows a severe microcytic anemia. Electrophoresis findings are remarkable for the absence of HbA and increased HbA<sub>2</sub> and HbF. Review of a newborn screen reveals the presence of only HbF. Beta thalassemia intermedia shows varying (but low) amounts of HbA on electrophoresis, depending on its severity. The iron status of children who have thalassemia can range from iron deficient (patients who have both iron deficiency and thalassemia) to normal. In cases of beta thalassemia major, if transfusion therapy has been initiated, patients may show excess iron (elevated ferritin and transferrin saturation).

**TREATMENT.** Children who have beta thalassemia trait require no treatment. Parents of children who have beta thalassemia trait should consider being tested for the disorder themselves. If both are carriers of a one-gene mutation (ie, both have beta thalassemia trait), there is a 25% chance of them having a child afflicted with a major beta thalassemia syndrome. After conception, chorionic villous sampling or amniocentesis allows prenatal diagnosis.

Patients who have beta thalassemia major require chronic RBC transfusions and suffer from the associated complications of iron overload, exposure to multiple RBC antigens, and potential exposure to blood-borne

pathogens. Bone marrow transplant from a matched donor is curative.

Depending on the severity of the mutations in the beta-globin genes, children who have beta thalassemia intermedia may require infrequent transfusion support or may have a clinical course indistinguishable from that of beta thalassemia major.

### Alpha Thalassemia

Four identical genes are responsible for the production of alpha-globin, two on each copy of chromosome 16. Mutations in these genes often result in stop codons, thus knocking out a gene's alpha-globin production entirely (ie, the gene is either normal and “on” or abnormal and “off”).

All four alpha-globin genes function in the normal state (Fig. 2). A one-gene defect results in “alpha thalassemia silent carrier” status, which is asymptomatic. Two gene defects lead to “alpha thalassemia trait.” The trait may be the result of one gene deleted on both chromosomes (“trans” deletions, more common in African-Americans) or two genes deleted on the same chromosome (“cis” deletions, more common in Asians). Affected children have microcytosis but often only mild (or no) anemia. This disorder should be suspected when there is microcytosis but no evidence of iron deficiency or beta thalassemia trait. Newborn screening programs may detect Bart hemoglobin (HbB) (heme associated with four gamma chains). Three gene deletions lead to hemoglobin H (HbH) disease. HbH is composed of heme associated with four beta chains, due to the paucity of alpha chains. This defect results in microcytic anemia,

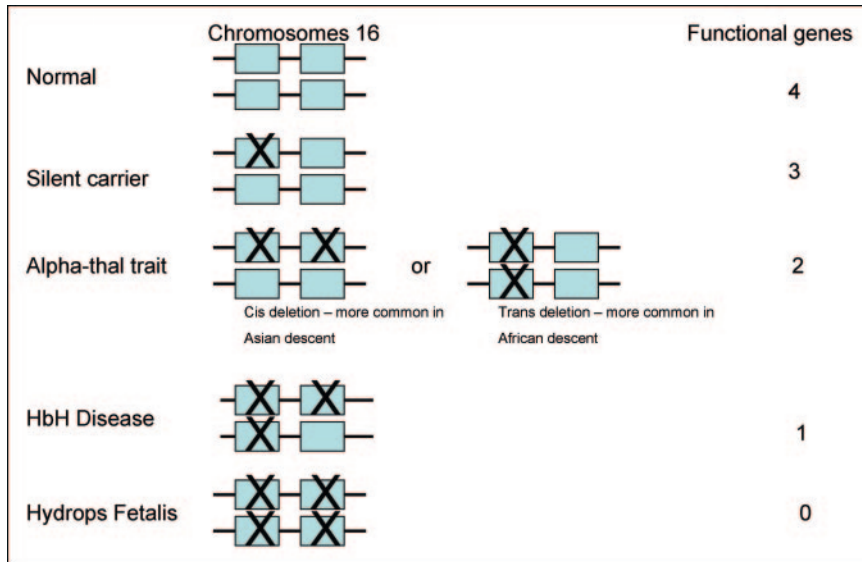


Figure 2. Gene deletions in alpha thalassemia syndromes.

chronic hemolysis, and splenomegaly. HbB is detected on a newborn screen. Finally, when all four alpha genes are defective, no normal hemoglobin can be made, even in utero. Hydrops fetalis (severe anemia with high-output cardiac failure and anasarca) results and almost always is fatal.

**LABORATORY FINDINGS.** Alpha thalassemia silent carrier state is associated with no abnormalities on a blood count. Alpha thalassemia trait is diagnosed most commonly when evaluation of a microcytic anemia shows no evidence of iron deficiency or of beta thalassemia trait. The hemoglobin electrophoresis pattern in patients having alpha thalassemia trait is normal. HbB, if present on a newborn screen, is helpful evidence of the disorder, but its absence does not rule out the condition.

Children who have HbH disease have significant microcytic anemia and demonstrate HbH on electrophoresis. Molecular studies of the ratio of beta chains to alpha chains are available (mean beta/alpha=1 in unaffected individuals, mean beta/alpha=1.3 for alpha thalassemia trait, mean beta/alpha=2.6 for HbH disease) but usually are unnecessary to make a diagnosis or provide counseling. Similarly, molecular testing for defective or absent alpha genes can be performed but usually is reserved for when results of the blood count and hemoglobin electrophoresis are inconclusive or when more extensive genetic counseling is needed.

**TREATMENT.** Silent carrier status and alpha thalassemia trait require no treatment. Because patients of Asian descent who have alpha thalassemia trait tend to have two genes affected on the same chromosome, they should be counseled on the potential risk of having children with a partner of similar ethnicity because the chance of having a baby who has a four-alpha gene deletion (hydrops fetalis) is increased. Children who have HbH disease may require folate supplements, periodic transfusions, or perhaps splenectomy; these patients should be followed by a pediatric hematologist. Infants who have hydrops fetalis/Bart hemoglobinopathy may be kept alive with lifelong transfusion therapy. A bone marrow transplant is curative and is the treatment of choice.

### Hemoglobinopathies With and Without Thalassemia

Hemoglobinopathies represent qualitative or functional defects of globins. Dozens of mutations in the genes for alpha- and beta-globin that lead to structural globin abnormalities have been described. Some mutations cause no significant microcytosis unless there is a concomitant defect in the amount of globin produced (ie, a thalassemia). The two primary severe hemoglobinopathy syndromes seen in the United States are homozygous SS disease and SC disease, both usually referred to as sickle cell disease. In homozygous SS disease, both beta-globin genes have a mutation that causes a substitution of valine for glutamate at amino acid position six on the beta-globin chain. In SC disease, one beta-globin chain has the S mutation and the other a C mutation (lysine substituted for glutamate at amino acid six). These two groups of patients have anemia but usually only mild microcytosis, if any. The diseases are associated with lifelong complications, including pain crises, overwhelming bacteremia, splenic sequestering of blood, gallstones, retinopathy, avascular necrosis of bones, acute chest syndrome, and stroke. SS and SC disease are suspected when a newborn screen reports the presence of HbS or HbC in the absence of HbA or there is a family history of sickle cell disease or sickle trait. When homozygous CC disease

**Table 4. Newborn Hemoglobin Electrophoresis Results\***

Hgb Pattern	Possible Diagnosis	Start Penicillin Prophylaxis <sup>†</sup>	Further testing and referral
FA	Normal	No	No
FAS	Sickle Trait	No	Family testing and counseling
FAC	C Trait	No	Family testing and counseling
FC	HbCC disease OR Cbeta <sup>0</sup>	No	Family testing and counseling, refer to hematology
FS	HbSS disease OR Sbeta <sup>0</sup>	Yes	Family testing and counseling, refer to hematology
FSC	HbSC disease	Yes	Family testing and counseling, refer to hematology
FSA	HbSbeta <sup>+</sup> thalassemia	Yes	Family testing and counseling, refer to hematology
FSV or FSD/G	Sickle with indeterminate hemoglobin pattern Some beta-globin chain variants in combination with HbS can be as severe as HbSS	Yes	Family testing and counseling, refer to hematology

\*By convention, hemoglobins are reported in order of decreasing concentration (eg, "FA" denotes more HbF than HbA)  
<sup>†</sup>Penicillin 125 mg twice a day, 62.5 mg twice a day for infants less than 3 kg  
 Adapted with permission from New England Pediatric Sickle Cell Consortium, 2002.

occurs, it is associated with a mild microcytic anemia and a relatively benign clinical course.

### Sickle Cell with Beta Thalassemia

In patients who have sickle-beta-thalassemia (Sbeta<sup>0</sup>), one beta-globin gene has the S mutation and the other is nonfunctioning. Sbeta<sup>0</sup> results in more significant microcytosis than homozygous SS disease, but the two disorders are identical clinically.

If a patient has one beta-globin gene with the S mutation and the other with a normal beta-globin gene that has decreased production, that individual is diagnosed as having Sbeta<sup>+</sup> thalassemia. The amount of normal beta-globin produced by the thalassemic gene determines disease severity. All affected patients have a microcytic anemia to some degree. If a significant amount of normal beta-globin is made, HbA (alpha<sub>2</sub>beta<sub>2</sub>) concentrations may be greater than 25%. Although somewhat protected by the presence of HbA, patients still are at risk for complications of sickle cell disease and should be followed by a hematologist. Similarly, a beta-globin gene that has the C mutation can be coupled with a beta-globin gene that has no activity (Cbeta<sup>0</sup>) or partial activity (Cbeta<sup>+</sup>). These disorders are clinically mild but do cause microcytic anemia.

**LABORATORY FINDINGS AND TREATMENT.** Sickle syndromes are diagnosed and defined best with hemoglobin electrophoresis, which determines the type and amount of hemoglobin present. Severe sickle/sickle-thalassemia syndromes (SS, SC, Sbeta<sup>0</sup>, Sbeta<sup>+</sup>) are diagnosed most often

by a newborn screen (Table 4). Hemoglobin electrophoresis should be repeated after 6 months of age to quantify the exact distribution of hemoglobin types and to define the patient's genotype better. It often is helpful to obtain hemoglobin electrophoreses on both parents, when possible.

Overwhelming infection with encapsulated organisms is the major cause of morbidity and mortality in children who have severe sickle disorders. Thus, even the suggestion of a severe sickle syndrome on a newborn screen (ie, HbS or HbS and HbC in the absence of HgbA) should lead to the immediate initiation of penicillin prophylaxis (penicillin G 125 mg by mouth tid) with referral to a hematologist (Table 3). Children who have a severe sickle/sickle-thalassemia syndrome require care from practitioners who are knowledgeable about the natural history, complications (some life-threatening), and unique health supervision needs associated with these diseases.

Milder sickle syndromes (CC, Cbeta<sup>0</sup>, Cbeta<sup>+</sup>) cause microcytic anemia, but do not require prompt initiation of penicillin prophylaxis. They do, however, warrant referral to a hematologist.

### Hemoglobin E

Hemoglobin E results from yet another mutation in the beta-globin gene. The condition is interesting in that the resulting globin chain has an abnormal structure (a globinopathy) *and* is produced in less-than-normal amounts (a thalassemia). The gene defect is most prevalent in southeast Asia, China, and the Indian subcontinent.

In the heterozygote state (Hb E-trait) (one normal beta-globin gene and one beta-globin gene with the E



mutation), there is microcytosis but only mild (or no) anemia. Because the normal beta-globin is made preferentially, HbA accounts for most of the hemoglobin produced. Affected patients are asymptomatic and require no treatment.

Patients who have two E mutations (homozygous HbE) produce almost all HbE along with some HbF and have a significant microcytosis with mild-to-moderate anemia.

When a child has one beta-globin gene with the E mutation and one beta-globin gene with a beta thalassemia mutation (HbE-beta thalassemia [Ebeta<sup>+</sup>]), the condition is more severe than if either were present alone. Affected patients can be clinically similar to those having beta thalassemia intermedia, with potentially significant microcytic anemia, depending on the amount of normal beta-globin that is produced.

**LABORATORY FINDINGS AND TREATMENT.** Hemoglobin electrophoresis distinguishes the different subtypes of HbE disease. HbE trait and HbEE require no treatment other than genetic counseling. Patients who have HbEbeta<sup>+</sup> likely need chronic transfusion support and iron chelation therapy; they also benefit from a hematologist's involvement.

### Lead Poisoning

Lead paint and leaded gasoline for cars were phased out of production in the 1970s, 1980s, and 1990s. However, many older homes contain residual lead paint. In addition, lead from auto emissions stays in soil for years, thus providing sources for lead poisoning. Also, certain hobbies, such as collecting leaden toy figures or using ceramic glazes that contain lead, may expose children to the metal. Lead can cause a microcytic anemia through two mechanisms. First, as a divalent metal, it interferes with iron absorption and utilization in normal iron pathways such as heme production (indeed, the microcytosis seen in lead poisoning is often due to iron deficiency). Second, lead can inhibit enzymes required for heme synthesis directly. Children who have lead poisoning may have pica either as a cause or symptom of lead poisoning.

#### Laboratory Findings and Treatment

Blood lead levels are easily measured. The Centers for Disease Control and Prevention and the American Academy of Pediatrics have published recommendations for testing, follow-up, and treatment that are posted at <http://aappolicy.aappublications.org/>.

### Anemia of Inflammation

Any inflammatory state, acute or chronic, can produce either normocytic or microcytic anemia, sometimes

called anemia of chronic disease. Cytokines such as interleukins-1 and -6; tumor necrosis factor-alpha; and interferon-alpha, -beta, and -gamma are produced in inflammatory states, including cancer, acute or chronic infection, and autoimmune disorders (eg, inflammatory bowel disease, juvenile idiopathic arthritis, connective tissue disease). These cytokines alter iron homeostasis, promoting accumulation of iron in storage sites (macrophages in the marrow and reticuloendothelial system) and inhibiting marrow RBC proliferation and differentiation. The result can be either micro- or normocytic anemia. The cause of inflammation is usually apparent in children who have this type of anemia. When there are no clinical signs of inflammation but laboratory findings suggest anemia of inflammation, checking for serologic markers of inflammation may be helpful.

#### Laboratory Findings and Treatment

In addition to microcytic anemia, inflammation typically produces an elevated ferritin level, elevated erythrocyte sedimentation rate, and increased C-reactive protein concentrations, but decreased serum iron concentrations and transferrin saturation. The underlying cause of inflammation should be addressed. Because children who have inflammation also may be iron deficient, iron status should be evaluated and iron replaced as needed. Severe anemia may require transfusions. The use of recombinant erythropoietin may be beneficial in some children who have chronic inflammation.

### Sideroblastic Anemia

The sideroblastic anemias are a rare group of disorders, some inherited and some acquired, that result from abnormal mitochondrial metabolism. This abnormality leads to ineffective heme synthesis and erythropoiesis. Unused iron is deposited in bone marrow erythroblasts and appears as rings around the nucleus ("ringed sideroblast"). Some of the sideroblastic anemias cause microcytic anemia. A sideroblastic anemia is diagnosed best with a bone marrow biopsy and warrants consultation with a hematologist.

### Summary

Microcytic anemia is the anemia encountered most commonly in pediatrics. Nutritional iron deficiency and beta thalassemia trait are the primary causes in pediatrics, and excessive cow milk consumption is a major cause of iron deficiency. The best method of diagnosing iron deficiency is to observe improvement in anemia and microcytosis with iron therapy. Beta thalassemia and sickle syndromes may not be clinically apparent until after 6 months of age. Families/patients who have thalassemia

(trait or major) should receive genetic counseling to understand their risks for having children who have severe forms of the disorder. Newborns found to have HbS or HbC on newborn screening should be started on penicillin immediately and referred to a hematologist.

### Suggested Reading

- Andrew NC. Medical progress: disorder of iron metabolism. *N Engl J Med.* 1999;341:1986–1995
- Bergeron J, Weng X, Robin L, Olney HJ, Soulieres D. Prevalence of alpha-globin gene deletions among patients with unexplained microcytosis in a North-American population. *Hemoglobin.* 2005;29:51–60
- Coyer SM. Anemia: diagnosis and management. *J Pediatr Health Care.* 2005;19:380–385
- Fleming RE, Bacon B. Orchestration of iron homeostasis. *N Engl J Med.* 2005;352:1741–1744
- Lo L, Singer ST. Thalassemia: current approach to an old disease. *Pediatr Clin North Am.* 2002;49:1165–1191
- 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:e51. Available at: <http://pediatrics.aappublications.org/cgi/content/full/105/4/e51>
- Rund D, Rachmilewitz E. Medical progress: beta-thalassemia. *N Engl J Med.* 2005;353:1135–1146
- Tyagi S, Pati HP, Choudhry VP, Saxena R. Clinico-haematological profile of HbE syndrome in adults and children. *Hematology.* 2004;9:57–60
- Weiss G, Goodnough LT. Medical progress: anemia of chronic disease. *N Engl J Med.* 2005;352:1011–1023

## PIR Quiz

Quiz also available online at [www.pedsinreview.org](http://www.pedsinreview.org).

1. A 14-month-old boy is brought to your office because a visiting relative noted that he appeared pale. He drinks 40 to 50 oz of cow milk daily. He looks well except for pallor. A complete blood count demonstrates a white blood cell count of  $6.9 \times 10^3/\text{mcl}$  ( $6.9 \times 10^9/\text{L}$ ), hemoglobin of 5.9 g/dL (59 g/L), mean cell volume of 57 fL, and platelet count of  $775 \times 10^3/\text{mcl}$  ( $775 \times 10^9/\text{L}$ ). The most appropriate next step is to:
  - A. Give a blood transfusion.
  - B. Give a single dose of intravenous iron.
  - C. Initiate a trial of oral ferrous sulfate.
  - D. Obtain hemoglobin electrophoresis.
  - E. Obtain serum ferritin, iron, and total iron-binding capacity measurements.
2. A 12-month-old girl is found to have a hemoglobin of 9.7 g/dL (97 g/L) during a health supervision visit. Other findings on the complete blood count are mean cell volume of 63 fL, red cell distribution width (RDW) of 15.1%, and red blood cell count of  $5.3 \times 10^3/\text{mcl}$  ( $5.3 \times 10^9/\text{L}$ ). She is given a trial of oral iron sulfate, and after 3 weeks, the hemoglobin measures 9.6 g/dL (96 g/L). The most likely explanation for the failure of the hemoglobin to increase is:
  - A. Administration of the oral iron with meals.
  - B. Failure to take oral iron.
  - C. Incorrect diagnosis.
  - D. Malabsorption of iron.
  - E. Ongoing blood loss.
3. An 18-month-old girl who was born in Cambodia and recently emigrated to the United States with her parents is brought to you because of pallor and abdominal distention. On physical examination, the girl is pale and quiet. Her spleen is palpable 8 cm below the left costal margin, and her liver is palpable 3 cm below the right costal margin. Among the laboratory findings are hemoglobin 4.1 g/dL (41 g/L), mean cell volume 58 fL, white blood cell count  $19.5 \times 10^3/\text{mcl}$  ( $19.5 \times 10^9/\text{L}$ ), and platelet count  $795 \times 10^3/\text{mcl}$  ( $795 \times 10^9/\text{L}$ ). The most likely diagnosis is:
  - A. E-beta thalassemia.
  - B. Hemoglobin H disease.
  - C. Iron deficiency.
  - D. Malaria.
  - E. Sickle-beta thalassemia.

(continued on page 14)

4. A 17-year-old girl of African descent had a complete blood count obtained in an emergency department because of high fever. She was told to follow-up with your office because of the findings on the test, which included hemoglobin 10.9 g/dL (109 g/L), mean cell volume 69 fL, white blood cell count  $9.5 \times 10^3$ /mL ( $9.5 \times 10^9$ /L) with 24% polymorphonuclear neutrophils, 70% lymphocytes, 6% monocytes, RDW 14.5%, and platelets  $395 \times 10^3$ /mL ( $395 \times 10^9$ /L). Hemoglobin electrophoresis demonstrates hemoglobin A 97%, hemoglobin A<sub>2</sub> 2.8%, and hemoglobin F 0.2%. The *most likely* cause of the anemia is:
- A. Alpha thalassemia silent carrier.
  - B. Alpha thalassemia trait.
  - C. Beta thalassemia intermedia.
  - D. Beta thalassemia trait.
  - E. Hemoglobin H disease.
5. A 4-year-old boy presents with a 4-week history of malaise and occasional low-grade fever. Results of laboratory studies include hemoglobin 9.5 g/dL (95 g/L), mean cell volume 68 fL, white blood cell count  $21.5 \times 10^3$ /mL ( $21.5 \times 10^9$ /L) with 65% polymorphonuclear neutrophils, 16% bands, 15% lymphocytes, and 4% monocytes, RDW 16.95%, and platelet count  $695 \times 10^3$ /mL ( $695 \times 10^9$ /L). Additional findings include serum iron 15 mcg/dL (2.7 mcmol/L), total iron-binding capacity 210 mcg/dL (37.6 mcmol/L), and serum ferritin 160 ng/mL (160 mcg/L). The *most likely* diagnosis is:
- A. Anemia of chronic disease.
  - B. Hemoglobin H disease.
  - C. Iron deficiency.
  - D. Lead poisoning.
  - E. Thalassemia trait.

**Microcytic Anemia**  
Matthew Richardson  
*Pediatrics in Review* 2007;28;5  
DOI: 10.1542/pir.28-1-5

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## Suggested Reading

- Bader-Meunier B, Armengaud JB, Haddad E, et al. Initial presentation of childhood-onset systemic lupus erythematosus: a French multicenter study. *J Pediatr*. 2005;146:648–653
- Brasington RD Jr. Immunologic rheumatologic disorders: systemic lupus erythematosus. *J Allergy Clin Immunol*. 2002;111(2 suppl):S593–S601
- Hsu S, Le EH, Khoshovis MR. Differential diagnosis of annular lesions. *Am Fam Physician*. 2001;64:289–296
- Klein-Gitilman M. Systemic lupus erythematosus in childhood. *Rheum Dis Clin North Am*. 2002;28:561–577
- Mikdashi J, Krumholz A, Handwerger B. Factors at diagnosis predict subsequent occurrence of seizures in systemic lupus erythematosus. *Neurology*. 2005;64:2102–2107
- Stichweh D, Arce E, Pascual V. Update on pediatric systemic lupus erythematosus. *Curr Opin Rheumatol*. 2004;16:577–587
- Taylor ML, Gill JM. Lupus and related connective tissue diseases. *Clin Family Pract*. 2005;7:209–224

### Clarification

In reference to the article on abnormalities in head size (*Pediatr Rev*. 2006;12:473–476), a reader has pointed out that offspring of mothers who have phenylketonuria can have features virtually identical to infants who have fetal alcohol syndrome, including microcephaly and classic facial dysmorphism. All mothers who have phenylketonuria are not significantly handicapped in their cognitive functions, making it more difficult to diagnose this disorder.

In the article on microcytic anemia (*Pediatr Rev*. 2007;28:5), the dose for prophylactic penicillin V in children younger than 5 years of age is given as 125 mg BID in a table and 125 mg TID in the text. The correct dose is 125 mg BID.

pelvis should be performed to search for an occult neoplasm. At least in some situations, early resection and immunosuppression may slow the development of bronchiolitis obliter-

ans, the leading cause of death in children afflicted with paraneoplastic pemphigus. (*Su-Ting T. Li, MD, MPH, University of California Davis, Sacramento, Calif.; Matthew*

*C. Hollander, MD, Wright-Patterson Air Force Base, Ohio)*

*To view Suggested Reading lists for these cases, visit [pedsinreview.org](http://pedsinreview.org) and click on Index of Suspicion*

### Clarification

In the January 2007 article entitled Microcytic Anemia (*PIR*. 2007;28:5–14), the mean hemoglobin value for a newborn is listed in Table 2 as 16.5 g/dL (165 g/L). In the same issue, the In Brief entitled Anemia and Polycythemia in the Newborn (pp 33–34) lists a value of 19.3 g/dL (193 g/L) as the normal newborn value. The discrepancy is due to the lower value applying to cord blood but the higher value representing the finding of a sample obtained from the baby after birth.

In “Index of Suspicion” Case 3 in the April 2007 issue (2007;28:139–145), the statement is made that hypercalcemia will cause a prolonged QT interval. A reader points out that although hypercalcemia may present infrequently with prolongation of the QT interval, it is more likely to manifest as a shortening of the QT interval. The authors agree.

## CORRECTIONS AND CLARIFICATIONS IN RESPONSE TO READER COMMENTS, 2007

Readers who send in their answers to the quiz questions using the paper answer sheet often add comments. Because those sheets sometimes are submitted long after the articles are published, publication of responses by authors can be delayed considerably. We present corrections and clarifications here that pertain to articles published in 2007 (volume 28).

**JANUARY.** In the article by Richardson on microcytic anemia (pages 5–14), question #2 presents a patient believed to have iron deficiency who does not respond to oral iron. The correct answer is given as *C. Incorrect diagnosis*. A reader questions whether answer *B. Failure to take oral iron* would be correct. Dr. Richardson replies, “Although *B* is a possibility, the Mentzer index suggests thalassemia trait (90% sensitive for beta thalassemia trait for values <13). The red blood cell distribution width may be mildly elevated in beta thalassemia and alpha thalassemia trait.” (Eldibany MM. Usefulness of certain red blood cell indices in diagnosing and differentiating thalassemia trait from iron-deficiency anemia. *Am J Clin Pathol*. 1999;111:676–682)

Question #4 gives the correct answer as *B. Alpha thalassemia trait*. A reader questions why the correct answer is not *D. Beta thalassemia trait*. Dr. Richardson replies, “Alpha thalassemia trait is more common in African American people than beta thalassemia trait and a nonelevated hemoglobin A2 value rules out beta thalassemia trait as the most common type. An unusual ‘delta-beta’ thalassemia or ‘silent carrier’ beta thalassemia hypothetically could be the answer, but the best answer is alpha thalassemia trait.”

**FEBRUARY.** In the article by Lewis on pediatric migraine (pages 43–53), 12 key diagnostic questions are listed; but questions #3 and #5 are identical. Dr. Lewis offers a new key question that can aid in distinguishing migraine from other primary headaches:

Are you having any other medical problems or are you being treated with any medications (for the headache or other purposes)?

**NOVEMBER.** In the article on seizures by Major and Thiele (pages 405–414), there is a discrepancy between the caption and the diagram in Figure 1, which shows scalp electrode placement in electroencephalography. The even-numbered electrodes should be placed over the right hemisphere, as indicated in the caption.

**NOVEMBER.** In the In Brief on hyponatremia by Farrell and Del Rio (pages 426–428), in Table 2, the third item in the left column should read, “Hypervolemic, increased intravascular volume<sup>4</sup>.”

**OCTOBER, 2008.** In the In Brief: Selecting Developmental Surveillance and Screening Tools (pages e52–e58), Table 2 lists screening instruments. One of the authors of the Modified Checklist for Autism in Toddlers (M-CHAT) provided a different URL for reviewing the most up-to-date information about the instrument, which is <http://www2.gsu.edu/~psydlr>.

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