

Microcytic Anemia

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Key Points

- The most common etiologies of microcytic anemia during childhood are iron deficiency and thalassemia.
- Iron deficiency anemia in toddlers is most often due to excessive cow's milk intake and treatment consists of reducing the amount of cow's milk in the diet to no more than 18-24 oz and oral iron supplementation.
- Thalassemia trait is prevalent among children of African, Asian, or Mediterranean descent and is often confused with iron deficiency anemia; however, it can be easily differentiated based on red blood cell count and indices.
- The most important management issue with thalassemia trait concerns appropriate genetic counseling.
- Referral to a pediatric hematologist should be considered in the cases of refractory iron deficiency, suspected thalassemia intermedia or major, suspected sideroblastic anemia or hemolytic anemia.

Definition, Assessment, and Diagnosis

Definition

- Microcytosis: Low Mean Corpuscular Volume (MCV) of red blood cells
 - The normal ranges for MCV are based on age, sex, and race and can be found in pediatric textbooks.
 - A general "rule of thumb" for lower limit of normal MCV (for children \geq 1 year up to

- puberty) is 70+ age (years).
 - Normal MCV for term neonates is 95-120fL.
- Anemia: Hemoglobin below the 2.5%ile for age, sex, and race
 - The normal ranges for hemoglobin can be found in pediatric textbooks.
 - A general “rule of thumb” for the lower limit of hemoglobin (for children ≥ 1 year up to puberty) is 11+ age in years multiplied by 0.1.
- Iron deficiency: Inadequate supply of iron in the body
 - May result from blood loss, low dietary iron intake, or a disease condition that inhibits iron uptake in the intestine
 - The prevalence of iron deficiency is highest in toddlers and adolescent females and ranges from 9% to 14%.
- Thalassemia: A group of inherited disorders that cause a reduction or absence of production of 1 or more globin chains which make up hemoglobin. Most common forms are alpha- and beta-thalassemia.
 - Alpha-thalassemia: Four genes control the production of alpha chains. One to 4 of the genes may be affected causing varying degrees of anemia and microcytosis.
 - One gene deletion alpha-thalassemia is known as “silent carrier” state. These patients show only minimally reduced MCV and no anemia.
 - Two gene deletion alpha-thalassemia is called “trait.” Patients may have a mild anemia and microcytosis.
 - Three gene deletion alpha-thalassemia is also known as “Hemoglobin H disease” (named for the increased Hemoglobin H or beta globin tetramers present). These patients have moderate-to-severe anemia that may cause symptoms and require chronic transfusions.
 - Four gene deletion alpha-thalassemia is called alpha-thalassemia major and without in utero blood transfusions, this condition is incompatible with life.
 - Beta-thalassemia: Two genes control beta globin gene synthesis.
 - Beta-thalassemia trait or minor occurs when there is one beta globin gene that does not produce normal amounts of beta globin chains. These patients are usually only mildly anemic with decreased MCV, but otherwise asymptomatic.
 - Beta-thalassemia intermedia occurs when beta globin production from both genes is disrupted. Patients with thalassemia intermedia have varying degrees of anemia and may require intermittent blood transfusions.
 - Beta-thalassemia major is a lack of beta globin production and causes a severe anemia requiring chronic transfusion support to survive.
- Sideroblastic anemia: A rare, inherited cause of microcytic anemia that occurs secondary to abnormal heme biosynthesis in the mitochondria leading to ringed sideroblasts
- Anemia of inflammation: Also known as anemia of chronic disease, it is a disorder of iron reutilization, which if severe, may cause microcytosis. The underlying pathophysiology is an increase in inflammatory cytokines, which increase production of hepcidin in the liver. Hepcidin then acts to block absorption of iron from the intestines and to block release of iron from storage macrophages.

Assessment

- History: A complete history should be performed.
 - Particular attention should be placed on dietary intake of iron rich foods and whole cow’s milk, prior response to iron, and blood loss.
 - All available prior blood counts should be reviewed to document chronicity of anemia and microcytosis.
 - To evaluate for possible hemolytic anemia, history should include episodes of jaundice

- (including neonatal) or scleral icterus and dark urine.
 - Transfusion history should be obtained.
- Family history: This should include anemia or thalassemia in immediate relatives. Patients with inherited hemolytic anemia may have family history of splenectomy, recurrent jaundice, or early gallstones.
- Physical exam
 - Complete physical exam should be performed to document evidence of pallor, jaundice or scleral icterus, adenopathy, hepatosplenomegaly, cardiac flow murmur, or signs of bleeding.
 - Vital signs may provide supporting evidence of the chronicity of the anemia since an acute drop in the hemoglobin should be accompanied by tachycardia with or without hypotension.
- Complete blood count: Complete blood count (CBC) should be evaluated with red cell indices. Reticulocyte count should also be obtained whenever possible. Red cell morphology may also give important clues to the etiology of the anemia.
- Other laboratory testing: Additional testing beyond CBC, reticulocyte and peripheral blood smear are rarely necessary to diagnose accurately most causes of microcytic anemia.
 - Iron studies: Ferritin, total iron binding capacity (TIBC), and serum iron levels may be helpful in evaluating more complex cases of iron deficiency anemia.
 - Hemoglobin electrophoresis: May be useful to diagnose some types of thalassemia or hemoglobinopathy. At a minimum, the newborn screen should be reviewed.
 - Family studies: In some difficult cases of thalassemia, CBC and hemoglobin electrophoresis on parents may be helpful.

Diagnosis

- Iron deficiency anemia: Iron deficiency anemia is the most common form of microcytic anemia in all age groups.
 - The cause is usually dietary secondary to excessive cow's milk intake in the toddler, but dietary causes are rare in the infant and adolescent.
 - Premature infants may present with dietary iron deficiency, if not supplemented, earlier during the first year of life due to lower iron stores at birth.
 - Blood loss is the most common etiology in the adolescent, especially in menstruating females.
 - Stool blood loss should be evaluated in any patient without a clear dietary cause.
 - Laboratory evaluation reveals a microcytic, hypochromic anemia usually with an increased red cell distribution width (RDW). Reticulocytopenia is present. Red blood cell (RBC) morphology may show marked anisopoikilocytosis in addition to the microcytosis and hypochromasia. Iron studies are rarely needed, but if obtained show low serum iron, low ferritin, and elevated TIBC.
- Thalassemia: In general, thalassemia is diagnosed based on a CBC showing microcytic anemia with a normal RDW. Reticulocytes may be normal or slightly elevated. Important in the diagnosis is that there is nearly always an elevated RBC count in patients with thalassemia. Red blood cell morphology generally reveals target cells or more marked anisopoikilocytosis for the more severe forms of thalassemia. Iron studies, if obtained, would be normal. Often with thalassemia trait, there is a prior history of anemia that failed to respond to iron therapy. [see Table 1]
 - Alpha-thalassemia may be diagnosed on the newborn screen if hemoglobin Bart's (gamma-chain tetramers) is detectable.
 - However, the silent carrier state and trait may not have hemoglobin Bart's reported on newborn screen and hemoglobin electrophoresis outside of the

newborn period will be normal.

- Patients with alpha-thalassemia will also have microcytosis present at birth if a CBC was obtained in the neonatal period. After the newborn period, the diagnosis of alpha-thalassemia is most often by exclusion. DNA sequencing of the alpha globin gene is possible for definitive diagnosis, but usually unnecessary and cost prohibitive.
- Beta-thalassemia may be diagnosed outside of the newborn period by hemoglobin electrophoresis showing elevated hemoglobin A₂.
 - Patients with beta-thalassemia have normal MCV at birth, but microcytosis becomes apparent around 6 months of age as they transition to adult hemoglobin A.
 - DNA probing or sequencing of the beta globin gene is possible for definitive diagnosis, but usually unnecessary and cost prohibitive.
- Anemia of inflammation
 - Generally, a source of inflammation is apparent when diagnosing anemia of inflammation, but if unclear, C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) may be helpful in detecting an underlying inflammatory state.
 - Complete blood count may show anemia with a mild microcytosis or normocytosis.
 - Often, with severe inflammatory states, concomitant iron deficiency is also present and makes diagnosis difficult.
 - In cases of clear-cut anemia of inflammation, iron studies should show low-to-normal serum iron, low-to-normal TIBC and elevated ferritin. Reticulocyte count is usually normal to low. Red blood cell morphology is usually normal.
- Other: Rarely microcytic anemia may be secondary to hemolysis. Microcytosis may be present in moderate-to-severe hereditary spherocytosis or other membranopathies. These conditions will have reticulocytosis and examination of peripheral smear should help make a definitive diagnosis.

Management

Iron deficiency anemia

The management of iron deficiency anemia requires proper identification of the underlying cause.

- Blood loss should be detected and managed as appropriate, e.g., oral contraceptive pills for menorrhagia or gastroenterology referral for occult blood in stool.
- Dietary counseling should be provided in cases of dietary deficiency of iron. Importantly, if excessive cow's milk intake is the cause, this must be reduced to no more than 18-24 oz cow's milk per day before iron supplementation will be successful.
- First line therapy for iron deficiency is oral iron supplementation.
 - High doses of elemental iron are initially required to correct the deficiency and prolonged therapy of up to 4-5 months is needed to replete iron stores.
 - Initial treatment dose is 3-6 mg/kg/day of elemental iron divided two times a day to three times a day.
 - Newer evidence in adults suggests more moderate doses of elemental iron once daily may be more efficacious.
 - The most readily available formulation is ferrous sulfate.
 - If appropriately treated and no ongoing blood loss is present, the hemoglobin should return to normal value within 4-6 weeks.
 - In those who fail to respond, after adherence has been assessed, referral to hematology is appropriate for evaluation of malabsorption or alternate diagnoses.

- Intravenous iron may also be appropriate for those intolerant to or refractory to oral iron, but should be administered by experienced hematologists given the potential for significant side effects.
 - Occasionally, a blood transfusion is appropriate for severe iron deficiency or severe anemia secondary to acute blood loss.
 - For children with chronic iron deficiency anemia, care must be taken to transfuse slowly packed red blood cells, as there is a risk of circulatory overload.
- Iron deficiency is a multi-system disorder which primarily causes anemia and its accompanying clinical sequelae, but cognitive and neurologic deficits are also prevalent.
 - Iron is required for the growth of all cells and plays a particularly important role in the central nervous system, including neuronal and glial metabolism, myelination, and production of neurotransmitters.
 - Iron deficiency may cause pica (and accordingly may contribute to increased lead burden), seizures, and, especially when present in children < 2 years of age have long-lasting, irreversible neurocognitive and behavioral consequences.
 - Therefore, it is imperative that iron deficiency, if not prevented, is promptly diagnosed and fully treated.

Thalassemia

- The most important aspect to manage thalassemia trait or minor is genetic counseling.
 - Patients with beta-thalassemia trait are at risk of having a child with sickle cell disease if his or her partner has sickle cell anemia or trait.
 - If his or her partner also has beta-thalassemia trait, there is a risk of a child with beta-thalassemia major or intermedia.
 - For alpha-thalassemia trait, there is a small risk of a child with hemoglobin H disease for the African-American population, but in the Southeast Asian population, genetic counseling should include discussion of the risk of alpha-thalassemia major in offspring.
- Patients with thalassemia should not be treated with iron as this therapy will not improve the anemia and may result in iron overload because persons with thalassemia have an increased rate of iron absorption at baseline.
- For those patients with suspected or confirmed thalassemia intermedia or major, referral to a hematology specialist for further evaluation and management is appropriate.

Anemia of inflammation

- In general, anemia of inflammation will normally improve as the inflammatory state recovers.
- Primary treatment should be aimed at treating the underlying condition. If concomitant iron deficiency is clearly present, the patient may partially respond to iron therapy, but otherwise iron therapy is not indicated for anemia of inflammation.
- For chronic inflammatory states, there may be a role for recombinant erythropoietin therapy or IV iron, but this should be used in consultation with an experienced hematologist.

Other

- If a hemolytic anemia or sideroblastic anemia is suspected, referral to a hematology specialist is advised for further evaluation and management.

Table 1: Classification of thalassemia syndromes based on clinical and laboratory features

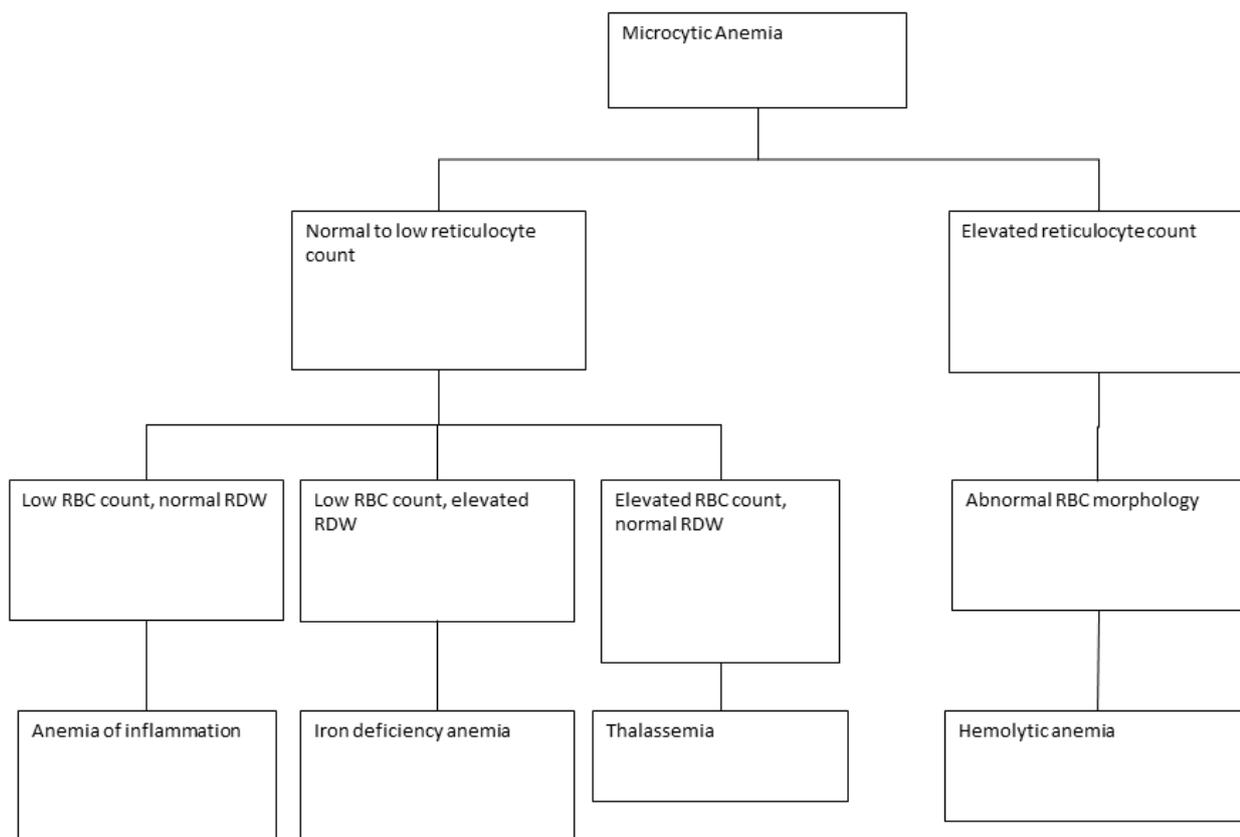
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Table 1: Classification of thalassemia syndromes based on clinical and laboratory features

Syndrome	Clinical features	Newborn screen pattern	Hemoglobin electrophoresis pattern ≥1 year of age
α-thalassemia syndromes			
Silent carrier (1 gene deletion)	No anemia, normal RBC	1-2% Hb Bart's (γ ₄)	Normal
Thalassemia trait (2 gene deletion)	Mild anemia, microcytosis	5-10% Hb Bart's (γ ₄)	Normal
Hemoglobin H (3 gene deletion)	Moderate anemia, microcytosis	>20% Hb Bart's (γ ₄)	5-30% HbH (β ₄)
Hydrops fetalis (4 gene deletion)	Death in utero caused by severe anemia	Mainly Hb Bart's (γ ₄)	NA
β-thalassemia syndromes			
Thalassemia minor	Mild anemia, microcytosis	Normal	Hb F 1-5%; Hb A ₂ 4-7%
Thalassemia intermedia	Moderate anemia, microcytosis	Normal	Hb F >20%; Hb A ₂ 2-5%
Thalassemia major	Severe anemia, microcytosis	Absent Hb A	Hb F ~100%; Hb A ₂ 2-5%

Figure 1. Evaluation of Microcytic Anemia

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This guideline was developed to improve health care access in Arkansas and to aid health care providers in making decisions about appropriate patient care. The needs of the individual patient, resources available, and limitations unique to the institution or type of practice may warrant variations.

References

References

1. Baker RD, Greer FR, Committee on Nutrition American Academy of Pediatrics. Diagnosis and Prevention of Iron Deficiency and Iron-Deficiency Anemia in Infants and Young Children (0-3 Years of Age). *Pediatrics* 2010;126(5):1040-50.
2. Cogswell ME, Looker AC, Pfeiffer CM, et al. Assessment of iron deficiency in US preschool children and nonpregnant females of childbearing age: National Health and Nutrition Examination Survey 2003-2006. *Am J Clin Nutr* 2009;89:1334-42.
3. Crary SE, Hall K, Buchanan GR. Intravenous iron sucrose for children with iron deficiency failing to respond to oral iron therapy. *Pediatr Blood Cancer* 2011;56:615-9.
4. Georgieff MK. Long-term brain and behavioral consequences of early iron deficiency. *Nutr Rev* 2011;69 Suppl 1:S43-8.
5. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. *Blood* 2010;116:4754-61.
6. Heeney MM. Anemia. In: Rudolph CD, Rudolph AM, Lister GE, First LR, et al, eds. *Rudolph's Pediatrics*. 22nd ed. New York: McGraw-Hill; 2011:1542-5.

7. Heeney MM. Iron Deficiency. In: Rudolph CD, Rudolph AM, Lister GE, First LR, et al, eds. Rudolph's Pediatrics. 22nd ed. New York: McGraw-Hill; 2011:1546-8.
8. Lozoff B, Georgieff MK. Iron deficiency and brain development. Semin Pediatr Neurol 2006;13:158-65.
9. Lozoff B, Beard J, Connor J, Barbara F, et al. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev 2006;64:S34-43;S72-91.
10. Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood 2015;126:1981-9.
11. Ziegler EE. Consumption of cow's milk as a cause of iron deficiency in infants and toddlers. Nutr Rev 2011;69 Suppl 1:S37-42.