

CHAPTER 150

Anemia

ETIOLOGY

The diagnosis of anemia is determined by comparison of the patient's **hemoglobin level** with age-specific and sex-specific normal values (see [Table 149.2](#)). The production of androgens at the onset of puberty in males causes them to maintain a normal hemoglobin value approximately 1.5–2 g/dL higher than females. The easiest quantitative definition of anemia is any hemoglobin or hematocrit value that is 2 standard deviations (SDs; 95% confidence limits) below the mean for age and sex. Anemia is often a manifestation of another primary process and may accentuate other organ dysfunction.

Anemias are classified based on the size and hemoglobin content of the cells ([Fig. 150.1](#)). **Hypochromic, microcytic anemia** is caused by an inadequate production of hemoglobin. The most common causes of this type of anemia are iron deficiency and thalassemia. **Normocytic anemia** is often seen in patients with a systemic illness that impairs adequate marrow synthesis of red blood cells (RBCs). **Macrocytic anemia** is seen in deficiencies of vitamin B₁₂ and/or folic acid. **Hemolytic diseases** are mediated either by disorders intrinsic or extrinsic to the RBC that increase RBC destruction. The most common RBC membrane disorders are **hereditary spherocytosis** and **hereditary elliptocytosis**. In both disorders, abnormalities of proteins within the cytoskeleton lead to malformed RBC shape and function. Numerous RBC enzyme deficiencies may lead to hemolysis, including **glucose-6-phosphate dehydrogenase (G6PD) deficiency** (common) and **pyruvate kinase deficiency** (rare). Extravascular hemolysis occurs with immune-mediated hemolysis when RBCs coated with antibodies or complement are phagocytosed by the reticuloendothelial system. Intravascular hemolysis occurs when antibody binding leads to complement fixation and lysis of RBCs, or mechanical cleavage secondary to intravascular fibrin stranding.

CLINICAL MANIFESTATIONS

Acute onset of anemia can result in a poorly compensated state, manifested as tachycardia, systolic flow murmur, dizziness, poor exercise tolerance, headache, excessive sleeping (especially in infants) or fatigue, irritability, poor feeding, and syncope. In contrast, chronic anemia often is exceptionally well tolerated in children because of their cardiovascular

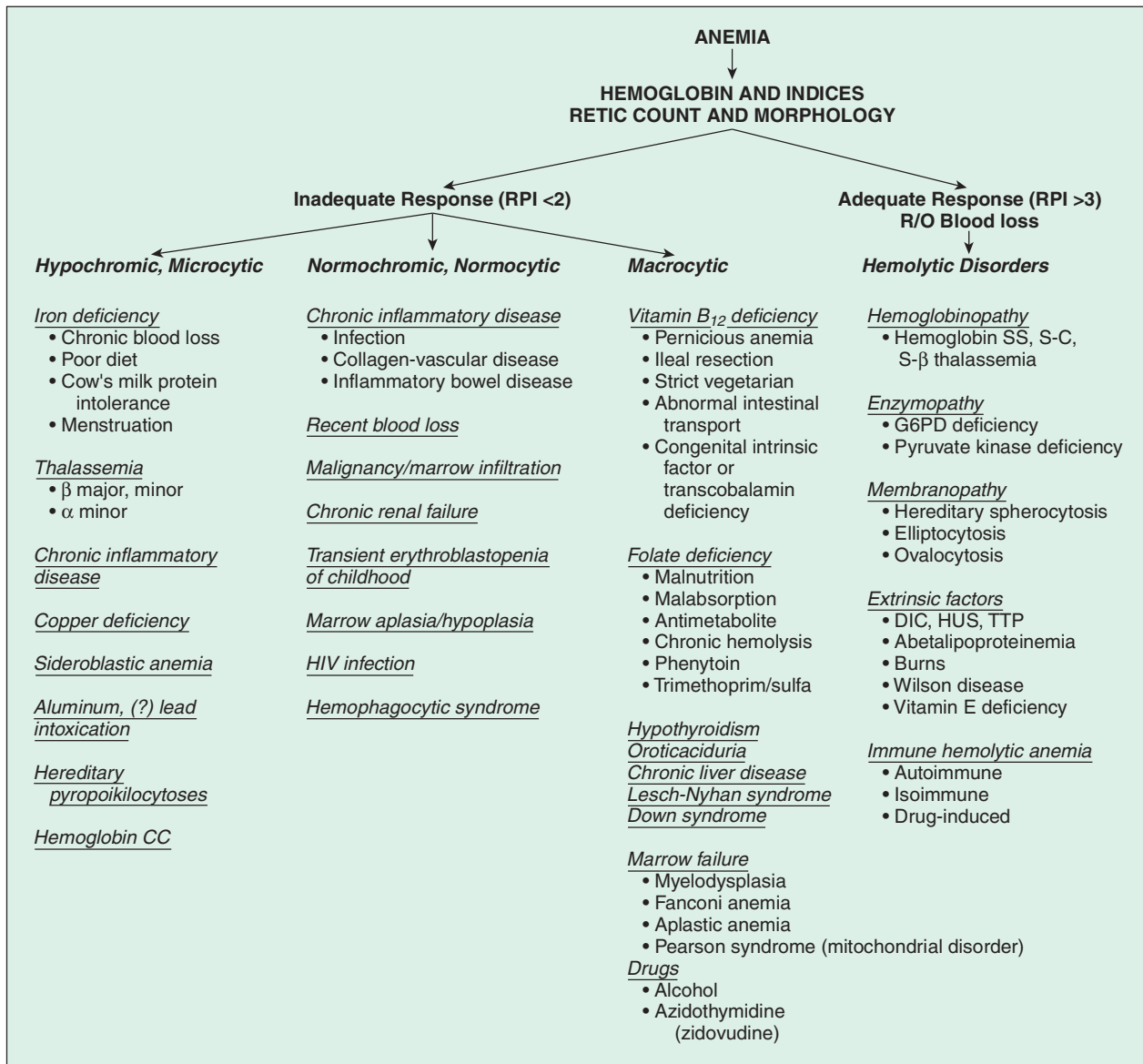


FIGURE 150.1 Use of the complete blood count, reticulocyte count, and blood smear in the diagnosis of anemia. *DIC*, Disseminated intravascular coagulation; *G6PD*, glucose-6-phosphate dehydrogenase; *HUS*, hemolytic uremic syndrome; *R/O*, rule out; *RPI*, reticulocyte production index; *TTP*, thrombotic thrombocytopenic purpura.

reserve. Usually, children with chronic anemia will have minimal tachycardia and a systolic flow murmur on examination. The urgency of diagnostic and therapeutic intervention, especially the use of packed RBC transfusion, should be dictated by the extent of cardiovascular or functional impairment more than the absolute level of hemoglobin.

The causes of anemia often can be suspected from a careful history adjusted for the patient's age (Tables 150.1 and 150.2). Anemia at any age demands a search for **blood loss**. A history of jaundice, pallor, previously affected siblings, drug ingestion by the mother, or excessive blood loss at the time of birth provides important clues to the diagnosis in newborns. A careful **dietary history** is crucial. A history of **jaundice, pallor**, and/or **splenomegaly** are often present with hemolytic anemia. Because of increased bilirubin production, **gallstones** (bilirubinate) are a common complication of chronic hemolysis.

Systemic complaints suggest acute or chronic illnesses as probable causes of anemia. In later childhood and adolescence, the presence of constitutional symptoms, unusual diets, drug ingestion, or blood loss, especially from menstrual bleeding, often points to a diagnosis. **Congenital hemolytic disorders** (e.g., enzyme deficiencies, membrane abnormalities) often present in the first 6 months of life and are frequently associated with neonatal jaundice, although these disorders often go undiagnosed when mild. A careful **drug history** is essential for detecting problems that may be drug induced. Pure dietary iron deficiency is rare except in children ages 1–3 years when cow's milk protein intolerance causes gastrointestinal blood loss and further complicates an already inadequate iron intake.

The physical examination may point to the potential cause (see Table 150.2). The **physiologic stability** of the patient may be compromised with both acute blood loss and

TABLE 150.1 Historical Clues in Evaluation of Anemia

VARIABLE	COMMENTS
Age	Iron deficiency rare in the absence of blood loss before 6 mo in term infants or before doubling of birthweight in preterm infants. Neonatal anemia with reticulocytosis suggests hemolysis or blood loss. Neonatal anemia with reticulocytopenia suggests bone marrow failure. Sickle cell anemia and β -thalassemia appear as fetal hemoglobin disappears (4–8 mo of age).
Family history and genetic considerations	X-linked: G6PD deficiency Autosomal dominant: spherocytosis Autosomal recessive: sickle cell anemia, Fanconi anemia Family member with history of cholecystectomy (for bilirubin stones) or splenectomy at an early age: spherocytosis or other inherited hemolytic anemias Ethnicity: thalassemia in persons of Mediterranean origin, African or Asian descent; G6PD deficiency in people of African, Greek, or Middle Eastern descent Race: β -thalassemia in persons of Mediterranean, African, or Asian descent; α -thalassemia in people who are Black or Asian; sickle cell disease in people who are Black
Nutrition	Cow's milk diet: iron deficiency Strict vegetarian: vitamin B ₁₂ deficiency Goat's milk diet: folate deficiency Pica: plumbism, iron deficiency Cholestasis, malabsorption: vitamin E deficiency
Drugs	G6PD: oxidants (e.g., nitrofurantoin, antimalarials) Immune-mediated hemolysis (e.g., penicillin) Bone marrow suppression (e.g., chemotherapy) Phenytoin, increasing folate requirements
Diarrhea	Malabsorption of vitamin B ₁₂ or E or iron Inflammatory bowel disease and anemia of inflammation with or without blood loss Milk protein intolerance–induced blood loss Intestinal resection: vitamin B ₁₂ deficiency
Infection	<i>Giardia lamblia</i> infection: iron malabsorption Intestinal bacterial overgrowth (blind loop): vitamin B ₁₂ deficiency Fish tapeworm: vitamin B ₁₂ deficiency Epstein-Barr virus, cytomegalovirus infection: bone marrow suppression, hemophagocytic syndromes <i>Mycoplasma</i> infection: hemolysis Parvovirus infection: bone marrow suppression HIV infection Chronic infection Endocarditis Malaria: hemolysis Hepatitis: aplastic anemia

G6PD, Glucose-6-phosphate dehydrogenase.

acute hemolysis, manifesting as tachycardia, blood pressure changes, and, most ominously, an altered state of consciousness. The presence of **jaundice** suggests hemolysis. **Petechiae** and **purpura** indicate a coagulopathy or systemic illness. **Hepatosplenomegaly** and **adenopathy** suggest infiltrative disorders such as leukemia. **Growth failure** or poor weight gain suggests anemia of inflammation (previously termed anemia of chronic disease). An essential element of the physical examination is the investigation of the stool for the presence of **occult blood**.

LABORATORY STUDIES

A hemoglobin or hematocrit test indicates the severity of the anemia. After anemia has been substantiated based upon age-adjusted normal values, the work-up should include a complete blood count with differential, platelet count, indices, and reticulocyte count. Examination of the peripheral blood smear is vital to assess the morphology of RBCs (Fig. 150.2), white blood cells (WBCs), and platelets. All cell lines should be scrutinized to determine whether anemia is the result of a process limited to the erythroid line or a process that affects other marrow elements. Using data obtained from the indices and reticulocyte count, the work-up can be organized on the basis of whether RBC production is adequate or inadequate and whether the cells are microcytic, normocytic, or macrocytic (see Fig. 150.1).

An appropriate bone marrow response to anemia includes an elevated absolute reticulocyte number, suggesting increased RBC production. This implies either hemolysis or blood loss. Anemia with a normal reticulocyte number suggests decreased or ineffective RBC production for the degree of anemia. Reticulocytopenia signifies either an acute onset of anemia such that the marrow has not had adequate time to respond, that reticulocytes are being destroyed in the marrow (antibody mediated), or that intrinsic bone marrow disease is present. The best indicators of the severity of hemolysis are the hemoglobin level and the elevation of the **reticulocyte count**. Biochemical evidence of hemolysis includes levels of bilirubin and lactate dehydrogenase and a decrease in haptoglobin.

DIFFERENTIAL DIAGNOSIS

Microcytic Anemia

Iron-Deficiency Anemia

Etiology

Infants fed cow's milk when younger than 1 year of age, toddlers fed large volumes of cow's milk, and menstruating adolescent females who are not receiving supplemental iron are at high risk for iron deficiency. **Dietary** iron-deficiency anemia is most common in bottle-fed toddlers who are receiving large volumes of cow's milk and eat minimal amounts of food high in iron content (see Chapters 28 and 31). Gastrointestinal blood loss can lead to iron-deficiency anemia and should be considered, especially in adolescent males. Iron-deficiency anemia also may be found in children with chronic inflammatory diseases, even without **chronic blood loss**.

Epidemiology

The prevalence of iron deficiency, the most common cause of anemia in the world, is approximately 9% in toddlers, 9–11%

TABLE 150.2 Physical Findings in the Evaluation of Anemia

SYSTEM/STRUCTURE	OBSERVATION	SIGNIFICANCE
Skin	Hyperpigmentation	Fanconi anemia, dyskeratosis congenita
	Café-au-lait spots	Fanconi anemia
	Vitiligo	Vitamin B ₁₂ deficiency
	Partial oculocutaneous albinism	Chediak-Higashi syndrome
	Jaundice	Hemolysis
	Petechiae, purpura	Bone marrow infiltration, autoimmune hemolysis with autoimmune thrombocytopenia, hemolytic uremic syndrome, hemophagocytic syndromes
	Erythematous rash	Parvovirus or Epstein-Barr virus infection
	Butterfly rash	SLE antibodies
	Bruising	Bleeding disorder, nonaccidental trauma, scurvy
Head	Frontal bossing	Thalassemia major, severe iron deficiency, chronic subdural hematoma
	Microcephaly	Fanconi anemia
Eyes	Microphthalmia	Fanconi anemia
	Retinopathy	Hemoglobin SS, SC disease (see Table 150.7)
	Optic atrophy	Osteopetrosis
	Blocked lacrimal gland	Dyskeratosis congenita
	Kayser-Fleischer ring	Wilson disease
	Blue sclera	Iron deficiency, osteopetrosis
Ears	Deafness	
Mouth	Glossitis	Vitamin B ₁₂ deficiency, iron deficiency
	Angular stomatitis	Iron deficiency
	Cleft lip	Diamond-Blackfan syndrome
	Pigmentation	Peutz-Jeghers syndrome (intestinal blood loss)
	Telangiectasia	Osler-Weber-Rendu syndrome (blood loss)
	Leukoplakia	Dyskeratosis congenita
Chest	Shield chest or widespread nipples	Diamond-Blackfan syndrome
	Murmur	Endocarditis: prosthetic valve hemolysis; severe anemia
Abdomen	Hepatomegaly	Hemolysis, infiltrative tumor, chronic disease, hemangioma, cholecystitis, extramedullary hematopoiesis
	Splenomegaly	Hemolysis, sickle cell disease, (early) thalassemia, malaria, leukemia/lymphoma, Epstein-Barr virus, portal hypertension
	Nephromegaly	Fanconi anemia
	Absent kidney	Fanconi anemia
Extremities	Absent thumbs	Fanconi anemia
	Triphalangeal thumb	Diamond-Blackfan syndrome
	Spoon nails	Iron deficiency
	Beau line (nails)	Heavy metal intoxication, severe illness
	Mees line (nails)	Heavy metals, severe illness, sickle cell anemia
	Dystrophic nails	Dyskeratosis congenita
Rectal	Hemorrhoids	Portal hypertension
	Heme-positive stool	Gastrointestinal bleeding
Nerves	Irritable, apathy	Iron deficiency
	Peripheral neuropathy	Deficiency of vitamins B ₁ , B ₁₂ , and E; lead poisoning
	Dementia	Deficiency of vitamins B ₁₂ and E
	Ataxia, posterior column signs	Vitamin B ₁₂ deficiency
	Stroke	Hemoglobin SS or Sp ⁰ -thalassemia, paroxysmal nocturnal hemoglobinuria
General	Small stature	Fanconi anemia, HIV infection, malnutrition

SLE, Systemic lupus erythematosus.

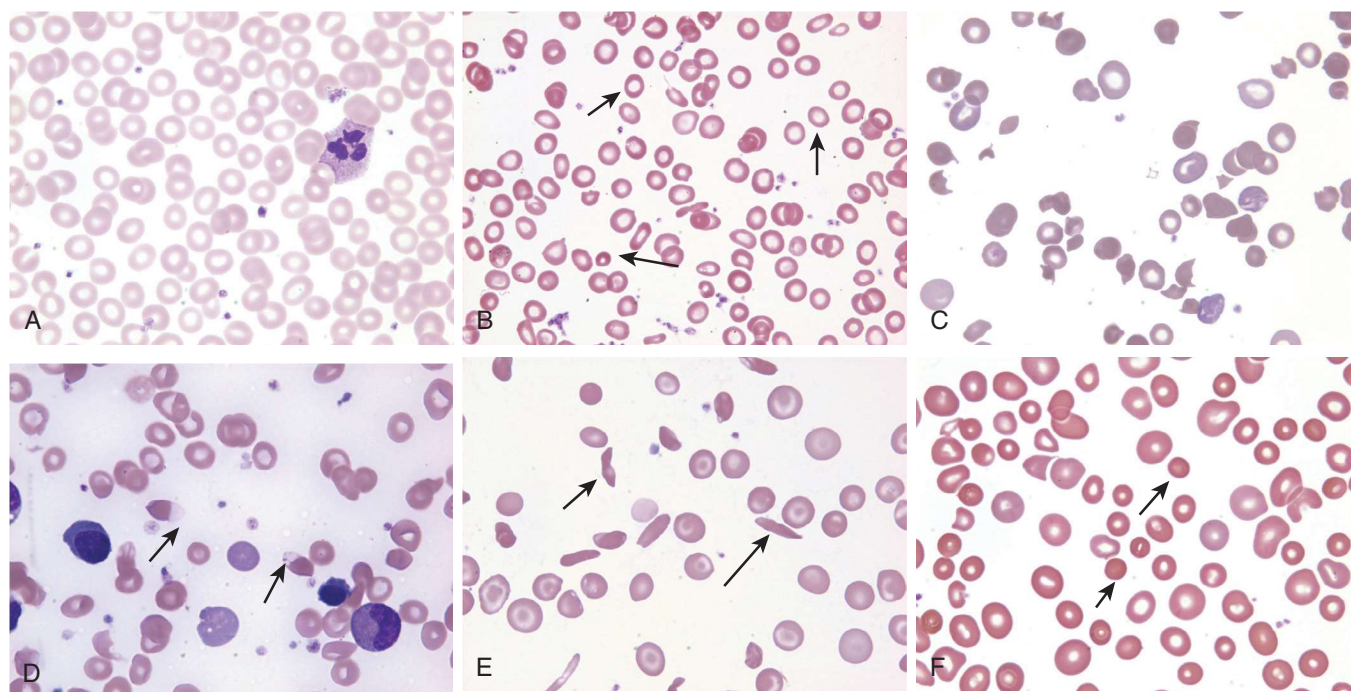


FIGURE 150.2 Morphologic abnormalities of the red blood cell. (A) Normal. (B) Hypochromic microcytes (iron deficiency). (C) Schistocytes (hemolytic uremic syndrome). (D) Blister cells (glucose-6-phosphate dehydrogenase deficiency). (E) Sickle cells (hemoglobin SS disease). (F) Spherocytes (autoimmune hemolytic anemia). Arrows represent the cell discussed. (Courtesy B. Trost and J.P. Scott.)

TABLE 150.3 Stages in Development of Iron Deficiency Anemia				
HEMOGLOBIN (g/dL)	PERIPHERAL SMEAR	SERUM IRON (μg/dL)	BONE MARROW IRON	SERUM FERRITIN (ng/ml)
13+ (normal)	nc/nc	50–150	Fe ²⁺	Male: 40–340 Female: 40–150
10–12	nc/nc	↓	Fe ²⁺ absent, erythroid hyperplasia	<12
8–10	hypo/nc	↓	Fe ²⁺ absent, erythroid hyperplasia	<12
<8	hypo/micro*	↓	Fe ²⁺ absent, erythroid hyperplasia	<12

*Microcytosis, determined by a mean corpuscular volume (in fL) <2 standard deviations (SD) below the mean, must be adjusted for age (e.g., –2SD at 3–6 mo = 74; at 0.5–2 yr = 70; at 2–6 yr = 75; at 6–12 yr = 77; and at 12–18 yr = 78).

Hypo/micro, Hypochromic, microcytic; hypo/nc, hypochromic, normocytic; nc/nc, normochromic, normocytic.

From Andreoli TE, Bennett JC, Carpenter CC, et al. Cecil Essentials of Medicine. 4th ed. Philadelphia: WB Saunders; 1997.

in adolescent females, and less than 1% in adolescent males. Iron-deficiency anemia occurs in approximately one-third of children who are iron deficient (Table 150.3). Children from low socioeconomic status in the United States may be at increased risk for iron deficiency because of poor dietary intake (see Chapter 31). Breast-fed infants are less likely to have iron deficiency than bottle-fed infants because, although there is less iron in breast milk, this iron is more efficiently absorbed. However, infants who continue to be exclusively breast-fed in the second half of the first year of life are at risk for iron deficiency.

Clinical Manifestations

In addition to cardiovascular manifestations of anemia, central nervous system (CNS) abnormalities (**apathy, irritability, poor concentration**) have been linked to iron deficiency,

presumably resulting from alterations of iron-containing enzymes (monoamine oxidase) and cytochromes. Poor muscle endurance, gastrointestinal dysfunction, and impaired WBC and T-cell function have been associated with iron deficiency. Iron deficiency in infancy may be associated with later **cognitive deficits** and poor school performance. The gradually developing nature of anemia associated with iron deficiency allows for physiologic compensation so that some children are minimally symptomatic even with severe anemia.

Treatment

In an otherwise healthy child, a **therapeutic trial of oral iron** is the best diagnostic study for iron deficiency as long as the child is re-examined and a response is documented. The response to oral iron includes rapid subjective improvement, especially in neurologic function (within 24–48 hours)

TABLE 150.4 Differentiating Features of Microcytic Anemias

TEST	IRON-DEFICIENCY ANEMIA	THALASSEMIA MINOR [†]	ANEMIA OF INFLAMMATION [‡]
Serum iron	Low	Normal	Low
Serum iron-binding capacity	High	Normal	Low or normal
Serum ferritin	Low	Normal or high	Normal or high
Marrow iron stores	Low or absent	Normal or high	Normal or high
Marrow sideroblasts	Decreased or absent	Normal or increased	Normal or increased
Free erythrocyte protoporphyrin	High	Normal or slightly increased	High
Hemoglobin A ₂ or F	Normal	High β -thalassemia; normal α -thalassemia	Normal
Red blood cell distribution width [§]	High	Normal	Normal/ $\uparrow$

*See Table 150.3 for definition of microcytosis.

[†] α -thalassemia minor can be diagnosed by the presence of Bart hemoglobin on newborn screening.

[‡]Usually normochromic; 25% of cases are microcytic.

[§]Red blood cell distribution width quantitates the degree of anisocytosis (different sizes) of red blood cells.

and reticulocytosis (48–72 hours); increase in hemoglobin levels (4–30 days); and repletion of iron stores (1–3 months). The usual therapeutic dose of 3–6 mg/day of elemental iron induces an increase in hemoglobin of 0.25–0.4 g/dL per day (a 1%/day increase in hematocrit). If the hemoglobin level fails to increase within 2 weeks after institution of iron treatment, careful re-evaluation for ongoing blood loss, development of infection, poor compliance, malabsorption, or other causes of microcytic anemia is required (Table 150.4; see Fig. 150.1).

Prevention

Bottle-fed infants should receive an iron-containing formula until 12 months of age. Exclusively breast-fed infants older than 6 months of age should receive an iron supplement. The introduction of iron-enriched solid foods at 6 months of age, followed by a transition to a limited amount of cow's milk and increased solid foods at 1 year, can help prevent iron-deficiency anemia. Adolescent females who are menstruating should have a diet enriched with iron-containing foods. A vitamin with iron may also be used.

Thalassemia Minor

Etiology and Epidemiology

α -thalassemia and β -thalassemia minor are common causes of microcytosis, either with or without a mild hypochromic, microcytic anemia. They are prevalent in certain ethnic groups (e.g., Mediterranean, Southeast Asian, African). Individuals of Asian descent are at risk of having three or four α genes deleted, resulting in hemoglobin H disease (β_4 tetramers) or hydrops fetalis, which is largely Bart (γ_4 tetramers) hemoglobin (Table 150.5 and Fig. 150.3).

Laboratory Testing

The thalassemia minor syndromes (i.e., α -thalassemia trait, β -thalassemia trait) are characterized by a mild hypochromic, microcytic anemia with a low absolute reticulocyte count (see Table 150.5) due at least in part to ineffective erythropoiesis. The RBC count is usually elevated. As a result, if the mean corpuscular volume (MCV) divided by the RBC count is less than 12.5 (Mentzer index), the diagnosis is suggestive of thalassemia trait.

The blood smear reveals only microcytosis with α -thalassemia minor. Outside the neonatal period, when Bart hemoglobin is no longer detectable, the hemoglobin electrophoresis is usually normal in α -thalassemia minor (see Fig. 150.3). Blood smears of patients with β -thalassemia minor also reveal microcytic RBCs. In addition, target cells and basophilic stippled RBCs, caused by precipitation of alpha chain tetramers, may also be present. The diagnosis of β -thalassemia minor is based on an elevation of hemoglobin A₂ and F levels. Molecular testing is indicated for identification of more severe or unusual variants.

Treatment

No treatment is required for children with **thalassemia minor**. However, children with more severe forms of thalassemia, such as β -thalassemia intermedia or major or children with hemoglobin H disease (β_4 tetramers), especially the Constant Spring variant, require chronic transfusion therapy (see Table 150.5).

Lead Poisoning

Lead poisoning may be associated with a hypochromic, microcytic anemia because most patients have concomitant iron deficiency due to competition for uptake between these two divalent cations. The history of living in an older home (built before 1980) with chipped paint or lead dust should raise suspicion of lead poisoning, especially in a child with **pica**. The lead content of water should also be assessed due to the potential for lead-containing pipes. **Basophilic stippling** on the blood smear is common. Lead intoxication rarely causes hemolytic anemia. Detection by routine screening, removal from exposure, chelation therapy, and correction of iron deficiency are crucial to the neurologic development of affected children.

Normocytic Anemia

Etiology and Treatment

Anemia is commonly seen in chronic inflammatory disease. Hepcidin, a protein made in the liver, plays a key role in iron homeostasis. Inflammation causes an increase in the production of hepcidin, interrupting the process of iron release by macrophages and the absorption of iron from the intestines

TABLE 150.5 Thalassemia Syndromes

DISORDER	GENOTYPIC ABNORMALITY	CLINICAL PHENOTYPE
β-THALASSEMIA		
Thalassemia major (Cooley anemia)	Homozygous β ⁰ -thalassemia	Severe hemolysis, ineffective erythropoiesis, transfusion dependency, hepatosplenomegaly, iron overload
Thalassemia intermedia	Compound heterozygous β ⁰ - and β ⁺ -thalassemia	Moderate hemolysis, splenomegaly, moderately severe anemia, but not transfusion dependent; main life-threatening complication is iron overload
Thalassemia minor	Heterozygous β ⁰ - and β ⁺ -thalassemia	Microcytosis, mild anemia
α-THALASSEMIA		
Silent carrier	α-/αα	Normal complete blood count
α-thalassemia trait	αα/- - (α-thalassemia 1, <i>cis</i> deletion) or α-/α- (α-thalassemia 2, <i>trans</i> deletion)	Mild microcytic anemia
Hemoglobin H	α-/- -	Microcytic anemia and mild hemolysis; not transfusion dependent*
Hydrops fetalis	-/- -	Severe anemia, intrauterine anasarca from congestive heart failure; death in utero or at birth

*The Constant Spring variant may require chronic transfusion.

From Andreoli T, Carpenter C, Griggs R, et al. Cecil Essentials of Medicine. 7th ed. Philadelphia: Saunders; 2007.

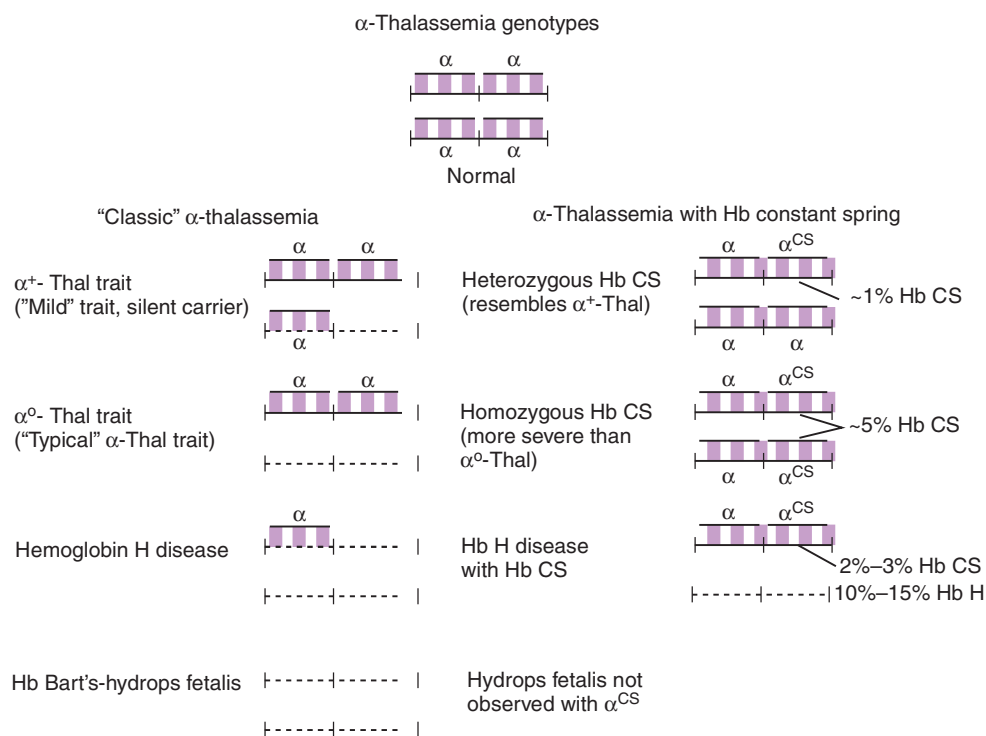


FIGURE 150.3 Genetic origins of the classic α-thalassemia syndromes due to gene deletions in the α-globin gene cluster. Hb Constant Spring (Hb CS) is an α-globin chain variant synthesized in such small amounts (1–2% of normal) that it has the phenotypic impact of a severe nondeletion α-thalassemia allele; however, the α^{CS} allele is always linked to a functioning α-globin gene, so it has never been associated with hydrops fetalis. (From Hoffman R, Benz EJ, Shattil SS, et al, eds. *Hematology: Basic Principles and Practice*. 5th ed. Philadelphia: Churchill Livingstone; 2008.)

leading to anemia. The **anemia of inflammation** may be normocytic or, less often, microcytic. This may pose a clinical challenge, when children with inflammatory disorders associated with blood loss (e.g., inflammatory bowel disease) exhibit a microcytic anemia. In these circumstances, only a bone marrow

aspiration with staining of the sample for iron can differentiate the two entities clearly (see Table 150.4). Low ferritin levels indicate concurrent iron deficiency. A trial of iron therapy is not indicated without a specific diagnosis in children who appear to be systemically ill.

TABLE 150.6 Differentiation of Red Blood Cell Aplasias and Pancytopenia

DISORDER	AGE AT ONSET	CHARACTERISTICS	TREATMENT
CONGENITAL			
Diamond-Blackfan syndrome (congenital hypoplastic anemia)	Newborn–1 mo; 90% of patients are <1 yr of age	Pure red blood cell aplasia, autosomal recessive trait, elevated fetal hemoglobin, fetal i antigen present, macrocytic, short stature, webbed neck, cleft lip, triphalangeal thumb; late-onset leukemia, mutation analysis	Prednisone, transfusion, hematopoietic stem cell transplant
ACQUIRED			
Transient erythroblastopenia of childhood (TEC)	6 mo–5 yr of age; 85% of patients are >1 yr of age	Pure red blood cell defect; no anomalies, fetal hemoglobin, or i antigen; spontaneous recovery, normal MCV	Expectant transfusion for symptomatic anemia
Idiopathic aplastic anemia (status posthepatitis, drugs, unknown)	All ages	All cell lines involved; exposure to felbamate, chloramphenicol, radiation	Hematopoietic stem cell transplantation, antithymocyte globulin, cyclosporine, androgens
FAMILIAL			
Fanconi anemia	Usually before 10 yr of age; mean is 8 yr	All cell lines; microcephaly, absent thumbs, café-au-lait spots, cutaneous hyperpigmentation, short stature; chromosomal breaks, high MCV and hemoglobin F; horseshoe or absent kidney; leukemic transformation; autosomal recessive trait	Androgens, corticosteroids, hematopoietic stem cell transplantation
Paroxysmal nocturnal hemoglobinuria	After 5 yr	Initial hemolysis followed by aplastic anemia; increased complement-mediated hemolysis; thrombosis; iron deficiency; CD59 low	Iron, hematopoietic stem cell transplantation, androgens, steroids, eculizumab
Dyskeratosis congenita	Mean is 10 yr for skin; mean is 17 yr for anemia	Pancytopenia; hyperpigmentation, dystrophic nails, leukoplakia; X-linked recessive; lacrimal duct stenosis; high MCV and fetal hemoglobin	Androgens, splenectomy, hematopoietic stem cell transplantation
Familial hemophagocytic lymphohistiocytosis	Before 2 yr	Pancytopenia; fever, hepatosplenomegaly, hypertriglyceridemia, CSF pleocytosis	Transfusion; often lethal; VP-16, hematopoietic stem cell transplantation, IVIG, cyclosporine
INFECTIOUS			
Parvovirus	Any age	Any chronic hemolytic anemia, typically sickle cell; new-onset reticulocytopenia and severe anemia	Red blood cell transfusion
Epstein-Barr virus (EBV)	Any age; usually <5 yr of age	X-linked immunodeficiency syndrome, pancytopenia	Transfusion, bone marrow transplantation
Virus-associated hemophagocytic syndrome (CMV, HHV-6, EBV)	Any age	Pancytopenia; hemophagocytosis in marrow, fever, hepatosplenomegaly	Transfusion, antiviral therapy, IVIG

CMV, Cytomegalovirus; CSF, cerebrospinal fluid; HHV-6, human herpesvirus 6; IVIG, intravenous immunoglobulin; MCV, mean corpuscular volume; VP-16, etoposide.

Bone marrow **infiltration by malignant cells** commonly leads to a normochromic, normocytic anemia. The mechanism by which neoplastic cells interfere with RBC and other marrow cell synthesis is multifactorial. The reticulocyte count is often low. Immature myeloid elements may be released into the peripheral blood because of the presence of the infiltrating tumor cells. An examination of the peripheral blood may reveal myelo- or lymphoblasts; when solid tumors metastasize to the marrow, these cells are seldom seen in the peripheral blood. Teardrop cells may be seen in the peripheral blood. A bone marrow examination is frequently necessary in the face of normochromic, normocytic anemia.

Congenital hypoplastic anemia (Diamond-Blackfan syndrome), a lifelong disorder, usually presents in the first few months of life or at birth with severe anemia and mild macrocytosis or normocytic anemia. This RBC disorder is due to a deficiency of bone marrow RBC precursors (Table 150.6). More than a third of patients have short stature. Many patients (50–66%) respond to corticosteroid treatment but must receive therapy indefinitely. Patients who do not respond to corticosteroid treatment are transfusion dependent and are at risk of the multiple complications of long-term transfusion therapy, especially iron overload. These patients have a higher rate of developing leukemia or other hematologic malignancies than the general population.

In contrast to the congenital hypoplastic anemias, **transient erythroblastopenia of childhood (TEC)**, a normocytic anemia caused by suppression of RBC synthesis, usually appears between 6 months and 5 years of age in an otherwise well-appearing child (see Table 150.6). Viral infections are thought to be the trigger, although the mechanism leading to RBC aplasia is poorly understood. The onset is gradual, but anemia may become severe. Transfusion of packed RBCs may be necessary if the anemia becomes symptomatic before recovery. Recovery is usually spontaneous. Mild neutropenia can be seen in patients with TEC; the well-appearing child with an otherwise normal physical exam helps differentiate from an underlying marrow infiltrative process. Differentiation from Diamond-Blackfan syndrome, in which erythroid precursors also are absent or diminished in the bone marrow, may be challenging.

Aplastic crises may complicate any chronic hemolytic anemia. Human parvovirus B19 (the cause of fifth disease) infects erythroid precursors and shuts down erythropoiesis. In children with chronic hemolytic anemia, these periods of severe reticulocytopenia can lead to an acute exacerbation of the anemia that may precipitate cardiovascular decompensation. Transient erythroid aplasia is without consequence in individuals with normal RBC survival. Recovery from parvovirus infection in hemolytic disease is spontaneous, but patients may need transfusion if the anemia is severe.

Macrocytic Anemia

See Fig. 150.1.

Marrow Failure/Pancytopenia

Etiology

Pancytopenia is a simultaneous quantitative decrease in formed elements of the blood—erythrocytes, leukocytes, and platelets. Patients more often exhibit symptoms of infection or bleeding than anemia because of the relatively short life span of WBCs and platelets compared with the life span of RBCs. Causes of pancytopenia include failure of production (implying intrinsic bone marrow disease), sequestration (hypersplenism), and increased peripheral destruction.

Differential Diagnosis

Features that suggest **bone marrow failure** and mandate an examination of the bone marrow include a low reticulocyte count, teardrop forms of RBCs (implying marrow replacement, not just failure), presence of abnormal forms of leukocytes or myeloid elements more immature than band forms, small platelets, and an elevated MCV in the face of a low reticulocyte count. Pancytopenia resulting from bone marrow failure is usually a gradual process, starting with one or two cell lines but later involving all three cell lines. Features suggesting **increased destruction** include reticulocytosis, jaundice, immature erythroid or myeloid elements on the blood smear, large platelets, and increased serum bilirubin and lactic dehydrogenase.

Aplastic Anemia

Etiology and Epidemiology

In a child with aplastic anemia, pancytopenia evolves as the hematopoietic elements of the bone marrow disappear and the marrow is replaced by fat. In developed countries, aplastic

anemia is most often idiopathic. The disorder may be induced by drugs such as chloramphenicol and felbamate or by toxins such as benzene. Aplastic anemia also may follow infections, particularly hepatitis and infectious mononucleosis (see Table 150.6). Immunosuppression of hematopoiesis is postulated to be an important mechanism in patients with postinfectious and idiopathic aplastic anemia.

Laboratory Studies

A **bone marrow aspirate and biopsy** are crucial to determine cellularity or the extent of depletion of the hematopoietic elements.

Treatment

Survival rate is approximately 20% in severe aplastic anemia with supportive care alone, although the duration of survival may be years when vigorous blood product and antibiotic support is provided. For children with severe aplastic anemia—defined by an absolute reticulocyte count less than 50,000/ μ L, absolute neutrophil count less than 500/ mm^3 , platelet count less than 20,000/ mm^3 , and bone marrow cellularity on biopsy specimen less than 25% of normal—the treatment of choice is **hematopoietic stem cell transplantation (HSCT)** from a sibling with identical human leukocyte antigen (HLA) and compatible mixed lymphocytes. When HSCT occurs before the recipient is sensitized to blood products, survival rate is greater than 80%. The treatment of aplastic anemia without an HLA-matched donor for HSCT is evolving, with two major options: potent immunosuppressive therapy or unrelated or partially matched HSCT. Data using immunosuppressive therapy with antithymocyte globulin, cyclosporine or tacrolimus, and corticosteroids in combination with hematopoietic growth factors have been encouraging. Such therapy is often toxic, and relapses often occur when therapy is stopped.

Fanconi Anemia

Etiology and Epidemiology

Fanconi anemia is a constitutional form of aplastic anemia that usually presents in the latter half of the first decade of life and may evolve over years. A group of genetic defects in proteins involved in **DNA repair** have been identified in Fanconi anemia, which is inherited in an autosomal recessive manner. The diagnosis is based on demonstration of increased chromosomal breakage after exposure to agents that damage DNA. The repair mechanism for DNA damage is abnormal in all cells in Fanconi anemia, which may contribute to the increased risk of malignancies. Acute leukemia develops in 10% of cases. Other malignancies that can occur include solid tumors of the head and neck, gastrointestinal tumors, and gynecologic tumors.

Clinical Manifestations

Patients with Fanconi anemia have numerous characteristic clinical findings (see Table 150.6).

Treatment

HSCT can cure the pancytopenia caused by bone marrow aplasia. Many patients with Fanconi anemia and approximately 20% of children with aplastic anemia seem to respond for a time to **androgenic therapy**, which induces masculinization and may cause liver injury and liver tumors. Androgenic

therapy increases RBC synthesis and may diminish transfusion requirements. The effect on granulocytes, and especially the platelet count, is less impressive.

Other less common etiologies of familial bone marrow failure resulting in pancytopenia are outlined in Table 150.6. These include dyskeratosis congenita and familial hemophagocytic lymphohistiocytosis.

Marrow Replacement

Marrow replacement may occur because of **leukemia**, **solid tumors** (especially neuroblastoma), **storage diseases**, **osteopetrosis** in infants, and **myelofibrosis**, which is rare in childhood. The mechanisms by which malignant cells impair marrow synthesis of normal hematopoietic elements are complex and incompletely understood. Bone marrow aspirate and biopsy are needed for precise diagnosis of the etiology of marrow synthetic failure.

Pancytopenia Resulting from Destruction of Cells

Pancytopenia resulting from destruction of cells may be caused by **intramedullary destruction** of hematopoietic elements (e.g., myeloproliferative disorders, deficiencies of folic acid and vitamin B₁₂) or by the **peripheral destruction** of mature cells. The usual site of peripheral destruction of blood cells is the spleen, although the liver and other parts of the reticuloendothelial system may contribute. **Hypersplenism** may be the result of anatomic causes (portal hypertension or splenic hypertrophy from thalassemia), infections (including malaria or Epstein-Barr virus [EBV]), storage diseases (Gaucher disease), or malignancy (lymphomas, histiocytosis). Splenectomy is indicated only when the pancytopenia is of clinical significance.

Hemolytic Anemias

Major Hemoglobinopathies

Alpha Chain Hemoglobinopathies

Etiology. Because alpha chains are needed for fetal erythropoiesis and production of hemoglobin F ($\alpha_2\gamma_2$), **alpha chain hemoglobinopathies** are present in utero. Four alpha genes are present on the two number 16 chromosomes (see Fig. 150.3 and Table 150.5). Single gene deletions produce no disorder (silent carrier state) but can be detected by measuring the rates of α and β synthesis or by using molecular biologic techniques. Deletion of two genes produces **α -thalassemia minor** with mild or no anemia and microcytosis. In individuals of African origin, the gene deletions occur on different chromosomes (*trans*). Thus infants born to parents that both have α -thalassemia gene deletions in *trans* have a benign disorder. In the Asian population, deletions may occur on the same chromosome (*cis*). Thus infants born to parents who both have α -thalassemia gene deletions in *cis* may inherit two number 16 chromosomes lacking three or even four genes resulting in severe disease. Deletion of three genes produces moderate hemolytic anemia with γ_4 tetramers (**Bart hemoglobin**) in the fetus and β_4 tetramers (hemoglobin H) in older children and adults (see Table 150.5). Deletion of all four α genes leads to hydrops fetalis, severe intrauterine anemia, and death, unless intrauterine transfusions are administered.

Beta Chain Hemoglobinopathies

Beta chain hemoglobinopathies are more prevalent in the United States than alpha chain disorders, possibly because these abnormalities are not symptomatic in utero. The major beta hemoglobinopathies include those that alter hemoglobin function (e.g., **hemoglobin S, C, E, and D**) and those that alter beta chain production (e.g., **β -thalassemias**). Because each RBC has two copies of chromosome 11 and they express both β -globin genes, most disorders of beta chains are not clinically severe, unless both beta chains are abnormal. By convention, when describing β -thalassemia genes, β^0 indicates a thalassemic gene resulting in absent beta chain synthesis, whereas β^+ indicates a thalassemic gene that permits reduced but not absent synthesis of normal β chains. Disorders of the beta chain usually manifest themselves clinically between 4 and 12 months of age when fetal hemoglobin nadirs unless they have been detected prenatally or by cord blood screening.

β -Thalassemia Major (Cooley Anemia)

Etiology and Epidemiology

β -thalassemia major is caused by mutations that impair **beta chain synthesis**. Because of unbalanced synthesis of alpha and beta chains, alpha chains precipitate within the cells, resulting in RBC destruction either in the bone marrow or in the spleen. β -thalassemia major is seen most commonly in individuals of Mediterranean or Asian descent. The clinical severity of the illness varies based on the specific molecular defect (see Table 150.5).

Clinical Manifestations

Signs and symptoms of β -thalassemia major result from the combination of chronic hemolytic anemia, decreased or absent production of normal hemoglobin A, and ineffective erythropoiesis. The anemia is severe and leads to growth failure and high-output heart failure. **Ineffective erythropoiesis** causes increased expenditure of energy and expansion of the bone marrow cavities of all bones, leading to osteopenia, pathologic fractures, extramedullary erythropoiesis with resultant hepatosplenomegaly, and an increase in the rate of iron absorption.

Treatment

Treatment of β -thalassemia major is based on a **hypertransfusion program** that corrects the anemia and suppresses the patient's own ineffective erythropoiesis, limiting the stimulus for increased iron absorption. This suppression permits the bones to heal, decreases metabolic expenditures, increases growth, and limits dietary iron absorption. Splenectomy may reduce the transfusion volume, but it adds to the risk of serious infection. Chelation therapy with deferasirox or deferoxamine should start when laboratory evidence of iron overload (**hemochromatosis**) is present and before there are clinical signs of iron overload (nonimmune diabetes mellitus, cirrhosis, heart failure, bronzing of the skin, and multiple endocrine abnormalities). HSCT in childhood, before organ dysfunction is induced by iron overload, has had a high success rate in β -thalassemia major and is the treatment of choice.

Sickle Cell Disease

Etiology and Epidemiology

The common sickle cell syndromes are **hemoglobin SS disease**, **hemoglobin SC disease**, **hemoglobin S- β^0 -thalassemia**, **hemoglobin S- β^+ -thalassemia**, and other rare variants (Table 150.7).

TABLE 150.7 Comparison of Sickle Cell Syndromes

GENOTYPE	CLINICAL CONDITION	PERCENT HEMOGLOBIN					OTHER FINDING(S)
		HB A	HB S	HB A ₂	HB F	HB C	
SA	Sickle cell trait	55–60	40–45	2–3	–	–	Usually asymptomatic
SS	Sickle cell anemia	0	85–95	2–3	5–15	–	Clinically severe anemia; Hb F heterogeneous in distribution
S-β ⁰ thalassemia	Sickle cell β ⁰ -thalassemia	0	70–80	3–5	10–20	–	Moderately severe anemia; splenomegaly in 50%; smear: hypochromic, microcytic anemia
S-β ⁺ thalassemia	Sickle cell β ⁺ -thalassemia	10–20	60–75	3–5	10–20	–	Hb F distributed heterogeneously; mild microcytic anemia
SC	Hb SC disease	0	45–50	–	–	45–50	Moderately severe anemia; splenomegaly; retinopathy; target cells
S-HPFH	Sickle-hereditary persistence of Hb F	0	70–80	1–2	20–30	–	Often asymptomatic; Hb F is uniformly distributed

From Andreoli T, Carpenter C, Griggs R, et al. Cecil Essentials of Medicine. 7th ed. Philadelphia: Saunders; 2007.

The specific hemoglobin genotype must be identified because the clinical complications differ in frequency, type, and severity. As a result of a single **amino acid substitution** (valine for glutamic acid at the β6 position), sickle hemoglobin crystallizes and forms a gel in the deoxygenated state. When reoxygenated, the sickle hemoglobin is normally soluble. The so-called reversible sickle cell can enter the microcirculation. As the oxygen is extracted and saturation declines, sickling may occur, occluding the microvasculature. The surrounding tissue undergoes infarction, inducing pain and chronic organ dysfunction. This sickling phenomenon is exacerbated by hypoxia, acidosis, fever, hypothermia, and dehydration.

Clinical Manifestations and Treatment

A child with sickle cell disease is vulnerable to **life-threatening infection** by 4 months of age due to splenic dysfunction. **Splenic dysfunction** is caused by sickling of the RBCs within the spleen, resulting in an inability to filter microorganisms from the bloodstream. Splenic dysfunction is followed, eventually, by **splenic infarction**, usually by 2–4 years of age. The loss of normal splenic function makes the patient susceptible to overwhelming infection by encapsulated organisms, especially *Streptococcus pneumoniae* and other pathogens (Table 150.8). The hallmark of infection is fever. A febrile child with sickle cell disease (temperature >38.5°C) must be evaluated immediately (see Chapter 96). Current precautions to prevent infections include prophylactic daily oral penicillin begun at diagnosis and vaccinations against pneumococcus, *Haemophilus influenzae* type b, meningococcus, hepatitis B virus, and influenza virus.

The anemia of hemoglobin SS disease is usually a chronic, moderately severe hemolytic anemia that is not routinely transfusion dependent. The severity depends in part on the patient's phenotype. Manifestations of chronic anemia include jaundice, pallor, variable splenomegaly in infancy, a cardiac flow murmur, and delayed growth and sexual maturation. Decisions about transfusion should be made based on the patient's clinical condition, the hemoglobin level, and the reticulocyte count.

Sickle cell disease is complicated by sudden, sometimes severe and life-threatening events caused by the acute intravascular sickling of the RBCs, with resultant pain or organ dysfunction (i.e., **crisis**). In two different clinical situations, an acute, potentially life-threatening decline in the hemoglobin level may be superimposed on the chronic compensated anemia. **Splenic sequestration crisis** is a life-threatening, hyperacute drop in the hemoglobin level (blood volume) secondary to splenic pooling of the patient's RBCs and sickling within the spleen. The spleen is moderately to markedly enlarged, and the reticulocyte count is elevated. In an **aplastic crisis**, parvovirus B19 infects RBC precursors in the bone marrow and induces transient RBC aplasia with reticulocytopenia and a rapid worsening of anemia because of the very short life span of sickle RBCs. Simple transfusion therapy is indicated for sequestration and aplastic crises when the anemia is symptomatic.

Acute vasoocclusive events may occur in any organ of the body and manifest as pain and/or significant dysfunction (see Table 150.8). The **acute chest syndrome** is a vasoocclusive event within the lungs with evidence of a new infiltrate on chest radiograph. It is often associated with infection and infarction. The patient may first complain of chest pain but within a few hours develops cough, increasing respiratory and heart rates, hypoxia, and progressive respiratory distress. Physical examination reveals areas of decreased breath sounds and dullness on chest percussion. Treatment involves early recognition and prevention of arterial hypoxemia. Oxygen, fluids, judicious use of analgesic medications, antibiotics, bronchodilators, and RBC transfusion (rarely exchange transfusion) are indicated as therapy for acute chest syndrome. *Incentive spirometry* may help reduce the incidence of acute chest syndrome in patients presenting with pain in the chest or abdomen.

Acute painful events are the most common type of vasoocclusive events. Pain usually localizes to the long bones of the arms or legs but may occur in smaller bones of the hands or feet in infancy (dactylitis), ribs, or in the abdomen. Painful events usually last 2–7 days. Repeated painful events within the femur may lead to avascular necrosis of the femoral head and chronic hip disease. Treatment of painful events includes

TABLE 150.8 Clinical Manifestations of Sickle Cell Disease

MANIFESTATION	COMMENTS
Anemia	Chronic, onset 3–4 mo of age; hemoglobin usually 6–10 g/dL
Aplastic crisis	Parvovirus infection, reticulocytopenia; acute and reversible; may need transfusion
Sequestration crisis	Massive splenomegaly (may involve liver), shock; treat with transfusion
Hemolytic crisis	May be associated with G6PD deficiency
Dactylitis	Hand-foot swelling in early infancy
Pain	Microvascular painful vasoocclusive infarcts of muscle, bone, bone marrow, lung, intestines; chronic pain (nervous system sensitization)
Cerebrovascular accidents (overt and silent)	Large and small vessel occlusion → thrombosis/bleeding (stroke); requires chronic transfusion; neurocognitive deficits
Acute chest syndrome	Infection, asthma, atelectasis, infarction, fat emboli, severe hypoxemia, infiltrate, dyspnea, absent breath sounds; treated with transfusions, antibiotics, oxygen, bronchodilators
Chronic lung disease	Pulmonary fibrosis, restrictive lung disease, cor pulmonale, pulmonary hypertension
Priapism	Causes eventual impotence; treated with transfusion, oxygen, or corpora cavernosa-to-spongiosa shunt
Ocular	Retinopathy
Gallbladder disease	Bilirubin stones; cholecystitis
Renal	Hematuria, papillary necrosis, renal concentrating defect; nephropathy
Cardiomyopathy	Heart failure
Skeletal	Osteonecrosis (avascular) of femoral or humeral head
Leg ulceration	Seen in older patients
Infections	Functional asplenia, defects in properdin system; pneumococcal bacteremia, meningitis, and arthritis; deafness from meningitis; <i>Salmonella</i> and <i>Staphylococcus aureus</i> osteomyelitis; severe <i>Mycoplasma pneumoniae</i>
Growth failure, delayed puberty	May respond to nutritional supplements
Psychosocial issues	Depression, anxiety, attention deficit hyperactivity disorder (ADHD)

*Clinical manifestations with sickle cell trait are unusual but include renal papillary necrosis (hematuria), sudden death on exertion, intraocular hyphema extension, and sickling in unpressurized airplanes.

G6PD, Glucose-6-phosphate dehydrogenase.

analgesia (usually opioids and nonsteroidal antiinflammatory drugs), and supplemental oxygen if the patient is hypoxic. Appropriate use of analgesics is imperative to control pain. Patients with sickle cell disease often require high doses of opioids due to tolerance to provide adequate pain control. The frequency of acute painful events increases with age. In

addition, chronic daily pain irrespective of an acute vasoocclusive event is associated with increasing age, occurring in 30–40% of adults and children. Chronic nervous system sensitization is likely a key driver of the chronic pain seen in patients with sickle cell disease.

Priapism occurs in males, usually older than 6 years of age. The child experiences a sudden, painful onset of a tumescent penis that will not relax. Therapeutic steps for priapism include the administration of oxygen, fluids, analgesia, and transfusion when appropriate to achieve a hemoglobin S less than 30%. Urgent partial exchange transfusion is often required to lower the hemoglobin S. Consultation with urology is recommended.

Overt **stroke** occurs in approximately 8–10% of patients with hemoglobin SS/hemoglobin S- β^0 -thalassemia disease. These events may present as the sudden onset of an altered state of consciousness, seizures, or focal paralysis. **Silent stroke**, which is defined as evidence of cerebral infarction on imaging studies but a normal neurologic examination, occurs in approximately 20% of patients with hemoglobin SS/hemoglobin S- β^0 -thalassemia disease. Neurocognitive changes such as a significant change in school performance or behavior is associated with silent stroke, and those with silent stroke are at increased risk for development of overt stroke. Children with hemoglobin SS/hemoglobin S- β^0 -thalassemia disease ages 2–16 years should be screened for increased risk of stroke using transcranial Doppler (TCD). Chronic monthly transfusions are indicated in those with overt stroke, silent stroke, and/or abnormal TCDs.

Laboratory Diagnosis

The diagnosis of hemoglobinopathies is made by identifying the precise amount and type of hemoglobin using **hemoglobin electrophoresis**, **isoelectric focusing**, or **high-performance liquid chromatography**. Every member of an at-risk population should have a precise hemoglobin phenotype performed at birth (preferably) or during early infancy. All U.S. states perform newborn screening for sickle cell disease.

Treatment

Disease-modifying therapy for sickle cell disease is evolving. Data support the use of chronic RBC transfusions in children who have had an overt or silent stroke or elevated TCD. Chronic RBC transfusions can also be used successfully for short time periods to prevent recurrent vasoocclusive events, including pain, acute chest syndrome, and priapism.

Hydroxyurea, which increases hemoglobin F, decreases the number and severity of painful events, frequency of acute chest syndrome, and need for transfusions in children as early as 1 year of age. Current published clinical care guidelines from the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) for patients with sickle cell disease recommend hydroxyurea should be initiated in asymptomatic children with severe sickle cell disease (HbSS or HbS- β^0 -thalassemia). Three new disease-modifying drugs have been Food and Drug Administration approved for the treatment of sickle cell disease in the past 2 years (i.e., crizanlizumab, voxelotor, L-glutamine). HSCT using a matched sibling donor has cured many children with sickle cell disease. HSCT using alternative donors for children, without a suitable sibling match, is being studied. Multiple approaches for gene therapy to treat sickle cell disease are also under investigation.

Supportive care for the treatment of end-organ complications (e.g., cardiopulmonary, renal) is vital to decrease morbidity.

Enzymopathies

Etiology

G6PD deficiency is an abnormality in the **hexose monophosphate shunt pathway** of glycolysis that results in the depletion of reduced nicotinamide adenine dinucleotide phosphate (NADPH) and the inability to regenerate reduced glutathione. When a patient with G6PD deficiency is exposed to significant oxidant stress, hemoglobin is oxidized, forming precipitates of sulfhemoglobin (**Heinz bodies**), which are visible on specially stained preparations.

The severity of hemolysis depends on the enzyme variant. In many G6PD deficiencies, the enzymes become unstable with aging of the RBC and cannot be replaced because the cell is anucleated. Older cells are most susceptible to oxidant-induced hemolysis. In other variants, the enzyme is kinetically abnormal.

Epidemiology

The most common variants of G6PD deficiency have been found in areas where malaria is endemic. G6PD deficiency protects against parasitism of the erythrocyte. The most common variant with normal activity is termed **type B** and is defined by its electrophoretic mobility. The approximate gene frequencies in Blacks are 70% type B, 20% type A, and 10% type A-. Only the **A- variant**, termed the *African variant*, is unstable. Ten percent of Black males are affected. A group of variants found in Sardinians, Sicilians, Greeks, Sephardic and Oriental Jews, and Arabs is termed the **Mediterranean variant** and is associated with chronic hemolysis and potentially life-threatening hemolytic disease. Because the gene for G6PD deficiency is carried on the X chromosome, clinical hemolysis is most common in males. Heterozygous females who have randomly inactivated a higher percentage of X chromosomes with the normal gene may become symptomatic, as may homozygous females with the A- variant (0.5–1% of females of African descent).

Clinical Manifestations

G6PD deficiency has two common presentations. Individuals with the A- variant have normal hemoglobin values when well but develop an **acute episode of hemolysis** triggered by serious (bacterial) infection or ingestion of an oxidant drug. The RBC morphology during episodes of acute hemolysis is striking, appearing to have “bites” taken out of them (cookie cells). These are areas of absent hemoglobin that are produced by phagocytosis of Heinz bodies by splenic macrophages; as a result, the RBCs appear blistered. Clinically evident jaundice, dark urine resulting from bilirubin pigments, hemoglobinuria when hemolysis is intravascular, and decreased haptoglobin levels are common during hemolytic episodes. Early on, the hemolysis usually exceeds the ability of the bone marrow to compensate, so the reticulocyte count may be low for 3–4 days.

Laboratory Studies

The diagnosis of G6PD deficiency is based on decreased NADPH formation. However, G6PD levels during an acute, severe hemolytic episode may be normal because the most deficient cells have been destroyed and reticulocytes are enriched with G6PD. Repeating the test at a later time when the patient

is in a steady-state condition, testing the mothers of boys with suspected G6PD deficiency, or performing electrophoresis to identify the precise variant present aids in diagnosis.

Treatment and Prevention

The treatment of G6PD deficiency is supportive. Transfusions are indicated when significant anemia associated with cardiovascular compromise is present. Maintaining hydration and urine alkalization protects the kidneys against damage from precipitated free hemoglobin. Hemolysis is prevented by avoidance of known oxidants, particularly long-acting sulfonamides, nitrofurantoin, primaquine, dimercaprol, and moth balls (naphthalene). Fava beans (favism) have triggered hemolysis, particularly in patients with the Mediterranean variant. Serious infection also is a potential precipitant of hemolysis in G6PD-deficient young children.

Pyruvate kinase deficiency is much less common than G6PD deficiency and represents a clinical spectrum of disorders caused by the functional deficiency of pyruvate kinase. Some individuals have a true deficiency state, and others have abnormal enzyme kinetics. The metabolic consequence of pyruvate kinase deficiency is adenosine triphosphate (ATP) depletion, impairing RBC survival. Pyruvate kinase deficiency is usually an autosomal disorder, and most children who are affected are double heterozygotes for two abnormal enzymes. Hemolysis is not aggravated by oxidant stress due to the profound reticulocytosis in this condition. Aplastic crises are potentially life threatening. The spleen is the site for RBC removal in pyruvate kinase deficiency. Most patients have amelioration of the anemia and a reduction of transfusion requirements after splenectomy.

Membrane Disorders

Etiology

The biochemical basis of **hereditary spherocytosis** and **hereditary elliptocytosis** is similar. Both conditions appear to have a defect in the protein lattice (spectrin, ankyrin, protein 4.2, band 3) that underlies the RBC lipid bilayer and provides stability of the membrane shape. In hereditary spherocytosis, pieces of membrane bud off as microvesicles because of abnormal vertical interaction of the cytoskeletal proteins and uncoupling of the lipid bilayer from the cytoskeleton. When the RBC loses membrane, cell shape changes from a biconcave disk to a spherocyte. This shape is less deformable when passing through narrow passages in the spleen. Hereditary elliptocytosis is a disorder of spectrin dimer interactions that occurs primarily in individuals of African descent. The transmission of hereditary spherocytosis can be autosomal dominant, autosomal recessive, or occur by a spontaneous mutation. **Hereditary pyropoikilocytosis** (unusual instability of the erythrocytes when they are exposed to heat at 45°C) is the result of a structural abnormality of spectrin.

Clinical Manifestations

Hereditary spherocytosis varies greatly in clinical severity, ranging from an asymptomatic, well-compensated, mild hemolytic anemia that may be discovered incidentally to a severe hemolytic anemia with growth failure, splenomegaly, and chronic transfusion requirements in infancy necessitating early splenectomy. The most common variant of hereditary elliptocytosis is a clinically insignificant morphologic abnormality

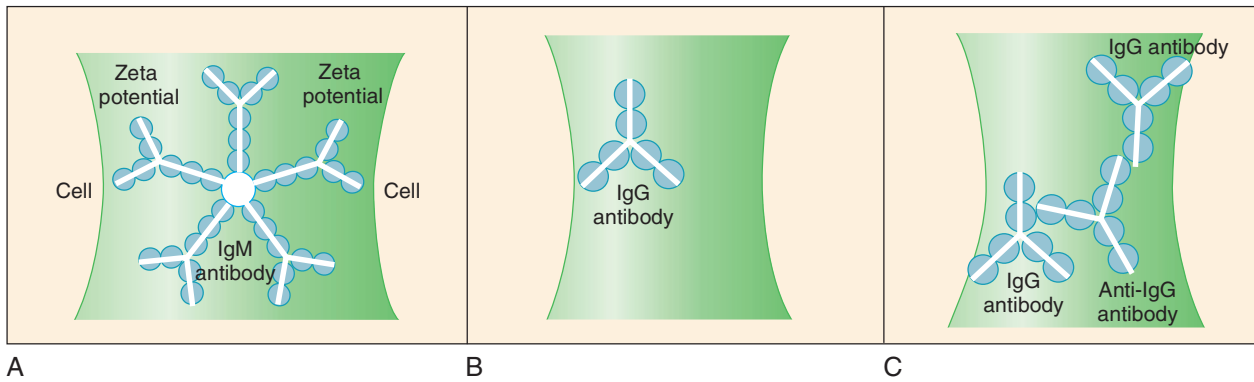


FIGURE 150.4 Coombs or direct antiglobulin test (DAT). In the DAT, so-called Coombs serum that recognizes human immunoglobulin (Ig) or complement (C) is used to detect the presence of antibody or C on the surface of the red blood cells (RBCs) by agglutination. (A) An IgM antibody can bind two RBCs simultaneously because of its multiple antigen-binding sites. The great size of the IgM allows it to bridge the surface repulsive forces (zeta potential) between RBCs and cause agglutination. (B) An IgG antibody is too small to bridge the zeta potential and cause agglutination. (C) On the addition of Coombs serum, the zeta potential is bridged successfully, and RBCs agglutinate. (Modified from Ware RE, Rosse WF. Autoimmune hemolytic anemia. In: Orkin SH, Nathan DG, Look AT, et al., eds. *Hematology of Infancy and Childhood*. 6th ed. Philadelphia: Saunders; 2003:530.)

without shortened RBC survival. The less common variant is associated with spherocytes, ovalocytes, and elliptocytes with a moderate, usually compensated, hemolysis. Far more significant hemolysis occurs in hereditary pyropoikilocytosis. The peripheral blood smear in hereditary pyropoikilocytosis often includes elliptocytes, spherocytes, fragmented RBCs, and striking microcytosis. Such patients may have bizarre blood smears in the newborn period with small, fragmented RBCs.

Laboratory Diagnosis

The clinical diagnosis of hereditary spherocytosis should be suspected in patients with even a few spherocytes found on the blood smear because the spleen preferentially removes spherocytes. An incubated **osmotic fragility test** confirms the presence of spherocytes and increases the likelihood of the diagnosis. The osmotic fragility test result is abnormal in any hemolytic disease in which spherocytes are present (e.g., in antibody-mediated hemolysis). Genetic studies (band 3 gene mutation) can also be done to confirm the diagnosis of hereditary spherocytosis.

Treatment

Splenectomy corrects the anemia and normalizes the RBC survival in patients with hereditary spherocytosis, but the morphologic abnormalities persist. Splenectomy should be reserved for children with severe hereditary spherocytosis and symptoms referable to chronic anemia or growth failure. Splenectomy should be deferred until age 5 years, if possible, to minimize the risk of overwhelming post-splenectomy sepsis and to maximize the antibody response to the polyvalent pneumococcal and meningococcal vaccine. In several reports, partial splenectomy seems to improve the hemolytic anemia and maintain splenic function in host defense.

Hemolytic Anemia Caused by Disorders Extrinsic to the Red Blood Cell

Etiology and Clinical Manifestations

Isoimmune hemolysis is caused by active maternal immunization against fetal antigens that the mother's erythrocytes

do not express (see Chapter 62). Examples are antibodies to the A, B, and Rh D antigens; other Rh antigens; and the Kell, Duffy, and other blood groups. Anti-A and anti-B hemolysis is caused by the placental transfer of naturally occurring maternal antibodies from mothers who lack A or B antigen (usually blood type O). Positive results of the direct antiglobulin (**Coombs**) test on the infant's RBCs (Fig. 150.4), the indirect antiglobulin test on the mother's serum, and the presence of spherocytes and immature erythroid precursors (erythroblastosis) on the infant's blood smear confirm this diagnosis. Isoimmune hemolytic disease varies in clinical severity. There may be no clinical manifestations or the infant may exhibit jaundice, severe anemia, and/or hydrops fetalis.

Autoimmune hemolytic anemia is usually an acute, self-limited Coombs-positive process that develops after an infection (e.g., *Mycoplasma*, EBV, or other viral infections) due to the production of autoantibodies that cause red cell destruction. Autoimmune hemolytic anemia may also be the presenting symptom of a chronic autoimmune disease (e.g., systemic lupus erythematosus, lymphoproliferative disorders, or immunodeficiency). Drugs may induce a Coombs-positive hemolytic anemia by forming a hapten on the RBC membrane (penicillin) or by forming immune complexes (quinidine) that attach to the RBC membrane. Antibodies then activate complement-induced intravascular hemolysis. The third type of drug-induced immune hemolysis occurs during treatment with α -methyl dopa and a few other drugs. In this type, prolonged drug exposure alters the RBC membrane, inducing neoantigen formation. Antibodies are produced that bind to the neoantigen; this produces a positive antiglobulin test result far more commonly than it induces hemolysis. In each of these conditions, the erythrocyte is an *innocent bystander*.

A second form of acquired hemolytic disease is caused by mechanical damage to the RBC membrane during circulation. In **thrombotic microangiopathy** the RBCs are trapped by fibrin strands in the circulation and physically broken by shear stress as they pass through these strands. Hemolytic uremic

syndrome, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura, malignant hypertension, toxemia, and hyperacute renal graft rejection can produce thrombotic microangiopathy. The platelets are usually large, indicating that they are young, but have a decreased survival, even if the numbers are normal. Consumption of clotting factors is more prominent in DIC than in the other forms of thrombotic microangiopathy. The smear shows RBC fragments (schistocytes), microspherocytes, teardrop forms, and polychromasia. Other examples of mechanical injury to RBCs include damage by exposure to nonendothelialized surfaces (as in artificial heart valves) or because of high flow and shear rates in giant hemangiomas (**Kasabach-Merritt syndrome**).

Alterations in plasma lipids, especially cholesterol, may lead to damage to the RBC membrane and shorten RBC survival. Lipids in the plasma are in equilibrium with lipids in the RBC membrane. High cholesterol levels increase the membrane cholesterol and the total membrane surface without affecting the volume of the cell. This condition produces **spur cells** that may be seen in abetalipoproteinemia and liver diseases. Hemolysis occurs in the spleen, where poor RBC deformability results in erythrocyte destruction. **Circulating toxins** (e.g., snake venoms and heavy metals) that bind sulfhydryl groups may damage the RBC membrane and induce hemolysis. Irregularly spiculated RBCs (burr cells) are seen in renal failure. **Vitamin E deficiency** can also cause an acquired hemolytic anemia because of abnormal sensitivity of membrane lipids to oxidant stress. Vitamin E deficiency may occur in premature infants who are not being supplemented with vitamin E or who have insufficient nutrition, in infants with severe malabsorption syndromes (including cystic fibrosis), and in infants with transfusional iron overload, which can lead to severe oxidant exposure.

Laboratory Diagnosis

The peripheral blood smear in autoimmune hemolytic anemia usually reveals spherocytes and occasionally nucleated RBCs. The reticulocyte count varies because some patients have relatively low reticulocyte counts because of autoantibodies that cross react with RBC precursors.

Treatment and Prognosis

Transfusion may be lifesaving in the management of autoimmune hemolytic anemia. Cross matching of RBCs in preparation for transfusion can be difficult since autoantibodies react with virtually all RBCs. In addition to **transfusion**, further management of autoimmune hemolytic anemia depends on antibody type. Acute management may involve administration of **corticosteroids** and, at times, **intravenous immunoglobulin**. Corticosteroids reduce the clearance of sensitized RBCs in the spleen. More than 80% of children with autoimmune hemolytic anemia recover spontaneously. In drug-induced hemolysis, withdrawal of the drug usually leads to resolution of the hemolytic process.

PEARLS FOR PRACTITIONERS

See Hematology: *Pearls for Practitioners* at the end of this section.