TABLE 47-9 THALASSEMIC SYNDROMES

DISORDER	GENOTYPIC ABNORMALITY	CLINICAL PHENOTYPE
β-THALASSEMIA		
Thalassemia major (Cooley's anemia)	Homozygous β^0-thalassemia	Severe hemolysis, ineffective erythropoiesis, transfusion dependency, iron overload
Thalassemia intermedia	Compound heterozygous β^0- and β^+-thalassemia	Moderate hemolysis, severe anemia, but not transfusion dependent; iron overload
Thalassemia minor	Heterozygous β^0- or β^+-thalassemia	Microcytosis, mild anemia
α-THALASSEMIA		
Silent carrier	α–/αα	Normal complete blood count
α-thalassemia trait	αα/— (α-thalassemia 1) *or* α–/α– (α-thalassemia 2)	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

Defective globin-chain synthesis in β-thalassemia causes both decreased normal hemoglobin production and the production of a relative excess of α chains. The decrease in normal hemoglobin synthesis results in a hypochromic anemia, and the excess α chains form insoluble α-chain complexes and cause hemolysis. In mild thalassemic syndromes, the excess α chains are insufficient to cause significant hemolysis, and the primary finding is a microcytic anemia. In severe forms of thalassemia, hemolysis occurs both in the periphery and in the marrow, with intense secondary expansion of the marrow production of RBCs. The expansion of the marrow space causes severe skeletal abnormalities, and the ineffective erythropoiesis also provides a powerful stimulus to absorb iron from the intestine.

The clinical spectrum of β-thalassemia reflects the heterogeneity of the molecular lesions causing the disease (see Table 47-9). β-Thalassemia major results from homozygous β^0-thalassemia, leading to severe hemolytic anemia; such patients are diagnosed in infancy and are transfusion dependent from birth. Patients with β-thalassemia intermedia also have two β-thalassemia alleles, but at least one of them is a mild β^+ mutation. These patients have severe chronic hemolytic anemia but do not require transfusions. Because of ineffective erythropoiesis, they patients chronically hyperabsorb iron and may develop iron overload in the absence of transfusions. β-Thalassemia minor is usually caused by heterozygous β-thalassemia, although it may reflect the inheritance of two mild thalassemic mutations. These are the patients in whom iron deficiency is often misdiagnosed. Iron studies show normal to increased iron with normal iron saturation. Documentation of a compensatory increase in HbA_2 and HbF on hemoglobin electrophoresis confirms the diagnosis.

α-Thalassemia

α-Thalassemia is almost always caused by mutations that delete one or more of the α-chain loci on chromosome 16. Four α-chain loci exist with two, almost identical, copies of the α-globin gene on each chromosome. The spectrum of α-thalassemia therefore reflects the lack of one, two, three, or all four α-globin genes (see Table 47-9). In general, the clinical manifestations of α-thalassemia are milder than those of β-thalassemia for two reasons. First, the presence of four α-chain genes allows for adequate α-chain synthesis unless three or four loci are deleted. Second, β-chain tetramers are more soluble than their α-chain counterparts and do not cause hemolysis. Patients with the loss of a single α-chain gene are silent carriers and have a normal hematocrit and MCV. Patients with deletion of two α chains, either on the same chromosome (––/αα, called α-thal 1) or on different chromosomes (α–/α–; α-thal 2), are microcytic and mildly anemic. Patients who inherit one α-thal 1 allele and one α-thal 2 allele (––/α–) have hemoglobin H disease. Hemoglobin H is the product of excess β-chain production, specifically β_4; it causes mild hemolytic anemia and minimal or no intramedullary erythrocyte destruction. Inheritance of the homozygous α-thal 2 allele results in no functional α-chain loci and is incompatible with life. The fetus is unable to make any functional hemoglobin beyond embryonic development because HbF also requires α chains. Free γ chains form tetramers, termed *hemoglobin Barts.* Hemoglobin Barts have an extremely high oxygen affinity, and failure to release oxygen in peripheral tissues results in severe congestive heart failure and anasarca, a clinical picture termed *hydrops fetalis.* Affected fetuses are stillborn or die soon after birth.

More information on the thalassemias, sickle cell disease, and other hemoglobinopathies can be found in Chapter 162, "The Thalassemias," and Chapter 163, "Sickle Cell Disease and Other Hemoglobinopathies," in Goldman-Cecil Medicine, *25th Edition.*

PROSPECTUS FOR THE FUTURE

Anemia is increasingly recognized as a marker of increased morbidity and mortality in adults with a wide range of medical conditions, including renal failure, malignancy, cardiac disease, inflammatory conditions, and other chronic diseases. Advances in understanding the pathophysiology of anemia of chronic inflammation are contributing to knowledge of iron metabolism and the roles cytokines play in hematopoiesis. These developments are paving the way for the development of new therapies for patients with anemia and iron overload. Ongoing progress in stem cell transplantation will contribute to the ability to treat the thalassemic syndromes and other hemoglobinopathies.

SUGGESTED READINGS

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Bennett CL, Silver SM, Djulbegovic B, et al: Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia, JAMA 299:914–924, 2008.