arterial saturation. Diagnostic evaluation for pneumonia and pulmonary embolism should be especially thorough, since these may occur with atypical symptoms. Critical interventions are transfusion to maintain a hematocrit >30, and emergency exchange transfusion if arterial saturation drops to <90%. As patients with sickle cell syndrome increasingly survive into their fifth and sixth decades, end-stage renal failure and pulmonary hypertension are becoming increasingly prominent causes of end-stage morbidity. A sickle cell cardiomyopathy and/or premature coronary artery disease may compromise cardiac function in later years. Sickle cell patients have received kidney transplants, but they often experience an increase in the frequency and severity of crises, possibly due to increased infection as a consequence of immunosuppression.

The most significant advance in the therapy of sickle cell anemia has been the introduction of hydroxyurea as a mainstay of therapy for patients with severe symptoms. Hydroxyurea (10–30 mg/kg per day) increases fetal hemoglobin and may also exert beneficial effects on RBC hydration, vascular wall adherence, and suppression of the granulocyte and reticulocyte counts; dosage is titrated to maintain a white cell count between 5000 and 8000/μL. White cells and reticulocytes may play a major role in the pathogenesis of sickle cell crisis, and their suppression may be an important side benefit of hydroxyurea therapy.

Hydroxyurea should be considered in patients experiencing repeated episodes of acute chest syndrome or with more than three crises per year requiring hospitalization. The utility of this agent for reducing the incidence of other complications (priapism, retinopathy) is under evaluation, as are the long-term side effects. To date, however, minimal risk of bone marrow dyscrasias or other neoplasms has been documented. Hydroxyurea offers broad benefits to most patients whose disease is severe enough to impair their functional status, and it may improve survival. HbF levels increase in most patients within a few months.

The antitumor drug 5-azacytidine was the first agent found to elevate HbF. It never achieved widespread use because of concerns about acute toxicity and carcinogenesis. However, low doses of the related agent 5-deoxyazacytidine (decitabine) can elevate HbF with more acceptable toxicity.

Bone marrow transplantation can provide definitive cures but is known to be effective and safe only in children. Clinical trials studying partially myeloablative conditioning regimens ("mini" transplants) are likely to support more widespread use of this modality in older patients. Prognostic features justifying bone marrow transplant are the presence of repeated crises early in life, a high neutrophil count, or the development of hand-foot syndrome. Children at risk for stroke can now be identified through the use of Doppler ultrasound techniques. Prophylactic exchange transfusion appears to substantially reduce the risk of stroke in this population. Children who do suffer a cerebrovascular accident should be maintained for at least 3–5 years on a program of vigorous exchange transfusion, as the risk of second strokes is extremely high.

Gene therapy for sickle cell anemia is being intensively pursued, but no safe measures are currently available. The development of newer methods of direct gene correction in situ (e.g., zinc finger nucleases, or "CRISPR" [clustered regularly interspaced short palindromic repeats] technology) could well find clinical use in these patients. Experimental methods of derepressing HbF by interfering with Bcl11a are also being explored.

UNSTABLE HEMOGLOBINS

Amino acid substitutions that reduce solubility or increase susceptibility to oxidation result in unstable hemoglobins that precipitate, forming inclusion bodies injurious to the RBC membrane. Representative mutations are those that interfere with contact points between the α and β subunits (e.g., Hb Philly [$\beta^{35Tyr\rightarrow Phe}$]), alter the helical segments (e.g., Hb Genova [$\beta^{28Leu\rightarrow Pro}$]), or disrupt interactions of the hydrophobic pockets of the globin subunits with heme (e.g., Hb Köln [$\beta^{98Val\rightarrow Met}$]) (Table 127-3). The inclusions, called *Heinz bodies*, are clinically detectable by staining with supravital dyes such as crystal violet. Removal of these inclusions by the spleen generates pitted, rigid cells that have shortened life spans, producing hemolytic anemia of variable severity, sometimes requiring chronic transfusion support. Splenectomy may be needed to correct the anemia. Leg ulcers and premature gallbladder disease due to bilirubin loading are frequent stigmata.

TABLE 127-3 REPRESENTATIVE ABNORMAL HEMOGLOBINS WITH ALTERED SYNTHESIS OR FUNCTION

Designation	Mutation	Population	Main Clinical Effects[a]
Sickle or S	$\beta^{6Glu\rightarrow Val}$	African	Anemia, ischemic infarcts
C	$\beta^{6Glu\rightarrow Lys}$	African	Mild anemia; interacts with HbS
E	$\beta^{26Glu\rightarrow Lys}$	Southeast Asian	Microcytic anemia, splenomegaly, thalassemic phenotype
Köln	$\beta^{98Val\rightarrow Met}$	Sporadic	Hemolytic anemia, Heinz bodies when splenectomized
Yakima	$\beta^{99Asp\rightarrow His}$	Sporadic	Polycythemia
Kansas	$\beta^{102Asn\rightarrow Lys}$	Sporadic	Mild anemia
M Iwata	$\beta^{87His\rightarrow Tyr}$	Sporadic	Methemoglobinemia

[a]See text for details.

Unstable hemoglobins occur sporadically, often by spontaneous new mutations. Heterozygotes are often symptomatic because a significant Heinz body burden can develop even when the unstable variant accounts for only a portion of the total hemoglobin. Symptomatic unstable hemoglobins tend to be β-globin variants, because sporadic mutations affecting only one of the four α globins alleles would generate only 20–30% abnormal hemoglobin.

HEMOGLOBINS WITH ALTERED OXYGEN AFFINITY

High-affinity hemoglobins (e.g., Hb Yakima [$\beta^{99Asp\rightarrow His}$]) bind oxygen more readily but deliver less O_2 to tissues at normal capillary Po_2 levels (Fig. 127-2). Mild tissue hypoxia ensues, stimulating RBC production and erythrocytosis (Table 127-3). In extreme cases, the hematocrits can rise to 60–65%, increasing blood viscosity and producing typical symptoms (headache, somnolence, or dizziness). Phlebotomy may be required. Typical mutations alter interactions within the heme pocket or disrupt the Bohr effect or salt-bond site. Mutations that impair the interaction of HbA with 2,3-BPG can increase O_2 affinity because 2,3-BPG binding lowers O_2 affinity.

Low-affinity hemoglobins (e.g., Hb Kansas [$\beta^{102Asn\rightarrow Lys}$]) bind sufficient oxygen in the lungs, despite their lower oxygen affinity, to achieve nearly full saturation. At capillary oxygen tensions, they lose sufficient amounts of oxygen to maintain homeostasis at a low hematocrit (Fig. 127-2) (*pseudoanemia*). Capillary hemoglobin desaturation can also be sufficient to produce clinically apparent cyanosis. Despite these findings, patients usually require no specific treatment.

METHEMOGLOBINEMIAS

Methemoglobin is generated by oxidation of the heme iron moieties to the ferric state, causing a characteristic bluish-brown muddy color resembling cyanosis. Methemoglobin has such high oxygen affinity that virtually no oxygen is delivered. Levels >50–60% are often fatal.

Congenital methemoglobinemia arises from globin mutations that stabilize iron in the ferric state (e.g., HbM Iwata [$\alpha^{87His\rightarrow Tyr}$], Table 127-3) or from mutations that impair the enzymes that reduce methemoglobin to hemoglobin (e.g., methemoglobin reductase, NADP diaphorase). Acquired methemoglobinemia is caused by toxins that oxidize heme iron, notably nitrate and nitrite-containing compounds, including drugs commonly used in cardiology and anesthesiology.

DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH UNSTABLE HEMOGLOBINS, HIGH-AFFINITY HEMOGLOBINS, AND METHEMOGLOBINEMIA

Unstable hemoglobin variants should be suspected in patients with nonimmune hemolytic anemia, jaundice, splenomegaly, or premature biliary tract disease. Severe hemolysis usually presents during infancy as neonatal jaundice or anemia. Milder cases may present in adult life with anemia or only as unexplained reticulocytosis, hepatosplenomegaly, premature biliary tract disease, or leg ulcers. Because spontaneous