Hematology Board Review Manual

STATEMENT OF EDITORIAL PURPOSE

The Hospital Physician Hematology Board Review Manual is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

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Hemoglobinopathies

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Hemoglobinopathies

Katharine Batt, MD, MSc, and Thomas Reske, MD

INTRODUCTION

Hemoglobin is a tetrameric protein composed of 2 pairs of globin chains (4 globin polypeptides) complexed with 4 heme groups. Each globin chain, or subunit, is associated with a heme group in its center. Globin chains are designated as α, β, γ, and δ and are classified as α chain or non–α chain. The dominant form of adult hemoglobin is hemoglobin A (HbA), which is made up of 2 α chains and 2 β chains.

α-Globin genes are encoded on chromosome 16, and the γ, δ- and β-globin genes are encoded on chromosome 11. Each individual carries a linked pair of α-globin genes: 2 from the paternal chromosome and 2 from the maternal chromosome. The synthesis and structure of the different globin chains is under tight genetic control, resulting in a 1.00 (± 0.05) ratio of α to non–α chains. Defects in these genes can cause the abnormal production of hemoglobin and anemias, disorders called hemoglobinopathies. These genetic defects can result in structural defects in the hemoglobin molecule, diminished production of the hemoglobin subunits, or abnormal association of subunits. Hemoglobinopathies can be qualitative (abnormal hemoglobin as in sickle cell disease), quantitative (anemia as in thalassemia), or both (sickle cell disease with concurrent thalassemia). Most hemoglobinopathies are not clinically apparent, while others produce abnormal laboratory findings and a few cause serious disease.

Structural defects in the hemoglobin molecule often occur because of mutations in either the α or β subunit chains, but mutations can also appear in the δ and γ chains. The most common clinically encountered qualitative mutation in the United States is hemoglobin S (HbS), a hemoglobinopathy characterized by an amino acid substitution at position 6 on the β chain, resulting in structurally abnormal sickle-shaped hemoglobin.

Mutations that cause diminished production of 1 of the 2 subunits of hemoglobin result in disorders called “thalassemias.” Mutations can affect any step in the pathway of globin gene expression, including transcription, pre-mRNA splicing, mRNA translation, mRNA stability, post-translational assembly, and stability of globin polypeptides. The 1.00 ratio of α to non–α chains is not maintained, and there is decreased production of total hemoglobin. Those hemoglobin molecules that are produced are structurally normal. Thalassemias are referred to by the deficient subunit: α-thalassemia or β-thalassemia. While the production of normal hemoglobin requires the linking of an α subunit with a β subunit to produce 1 of 2 dimers, in the case of an extreme lack of potential subunit partners, like subunits will abnormally associate. In the case of severe α-thalassemia, the β-globin subunits associate into groups of 4 (tetramers). In severe β thalassemia, α subunits do not self-associate and are rapidly degraded. The amount of affected globin determines the clinical picture and is epomorphic for the phenotypes thalassemia minor, thalassemia intermedia, and thalassemia major.

CLASSIFICATION

Hemoglobinopathies have no universal classification. By convention, hemoglobinopathies are classified according to the qualitative nature of the resultant hemoglobin (ie, sickle cell disease) and the quantitative amount of hemoglobin produced (ie, thalassemia).

The first attempt at classification dates back to the 1950s, when sickle cell hemoglobin was found to migrate differently from normal hemoglobin in an electric field, implying a different ionic charge. Hemoglobin A, or HbA, referred to normal adult hemoglobin, and hemoglobin S, or HbS, referred to sickle hemoglobin. Fetuses were known to have alkali-resistant hemoglobin, which is referred to as hemoglobin F (HbF). Inherited methemoglobinemia had been described by some Japanese investigators, so M was reserved for such hemoglobin variants. The next variant described was hemoglobin C (HbC), which has 2 more positive charges per tetramer than HbS and therefore migrates more slowly at alkaline pH. Hemoglobins D and G (the latter α variants) migrate in a fashion very similar to HbS. Hemoglobin J and hemoglobin I have 2 and 4 charges per tetramer electronegative to HbA, respectively, and thus migrate faster than HbA. As the discovery of variants continued, it became clear that the alphabet would be exceeded.
and thus the place of discovery (hemoglobin Edmonton) or the family name of an index case (hemoglobin Lepore) was used.

The advent of sophisticated sequencing technique allows the exact amino acid substitution on the affected chain to be added to the name of the hemoglobin variant. For example, HbS α6Glu→Val indicates that valine is substituted for glutamic acid in the sixth position of the β chain. More than 700 structural hemoglobin variants have been described in the literature.1 Within these broad categorizations, hemoglobinopathies are often further subdivided by high and low oxygen affinity and physical instability.

Disease manifestation depends largely on the genetic penetrance of the mutation. Heterozygous inheritance often results in either a clinically silent state or mild disease. Homozygous inheritance, however, may be associated with more severe disease. Homozygous hemoglobin variants are referred to as disease; heterozygous variants are usually termed traits. Homozygous HbC disease is also referred to as hemoglobin CC, while heterozygous HbC trait can be described as hemoglobin AC.

Hemoglobinopathies were traditionally detected on the basis of ionic charge differences imparted by amino acid substitutions; however, certain important variants are electrophoretically silent because the amino acid substitution does not alter the net charge. Quantitation of hemoglobin can provide valuable information as to the hemoglobin variant in question. Hemoglobin A2 (HbA2, consisting of 2 α and 2 δ chain) is most often elevated in β-thalassemia trait and decreased in some α-thalassemias and severe iron deficiency. Combination variants that comigrate with other hemoglobins can be further delineated by isoelectric focusing or high performance chromatography. In qualitative hemoglobinopathies, mutations can appear in any of the 4 different hemoglobin chains. Table 1 displays representative qualitative hemoglobin chain mutations.

Deoxygenation of the red cells of persons homozygous for the HbS gene results in aggregation of HbS molecules into chains, or microfibrils, that stiffen the red cells and stretch them into the classic sickle shape. In this process, the membranes become permeable to water and potassium, resulting in cellular dehydration. The deranged membranes also interact with adhesion molecules in the plasma, making the sickle cells adhere to one another as well as to the vascular endothelium, thus causing vaso-occlusion. Red cell hemolysis also occurs. End organ damage develops from episodes of intermittent vascular clogging and tissue ischemia. Most of the pain is due to vaso-occlusion of bone, where the low shear forces of sinusoidal blood flow are less apt to disrupt cellular aggregation than in other vascular beds. Inflammation precipitates painful vaso-occlusive episodes. The dilution of HbS by HbA in sickle cell trait makes the red blood cells resistant to sickling at the oxygen tensions prevailing in most parts of the body most of the time. Table 2 outlines the common clinical and hematologic findings in the common variants of sickle cell disease.

Quantitative hemoglobin disorders, or thalassemias, are classified according to the deficient globin chain. α-Thalassemia results from deletion of 1 or more of the 4 α-chain genes. Any genetic variant that decreases or increases the number of unpaired α chains can modify the phenotype; this applies to compound heterozygotes as well as homozygotes. The severity of disease is directly correlated to the number of genes deleted. Patients with 2 deleted or inactivated α chains present with borderline hypochromic, microcytic anemia, whereas patients with one functional α gene, known as hemoglobin H, have moderate to severe hemolytic anemia. As α chains are present in fetal and adult hemoglobin, α-chain

<table>
<thead>
<tr>
<th>Hemoglobin Variants</th>
<th>Position</th>
<th>Substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbS</td>
<td>6</td>
<td>Glutamic acid → Valine</td>
</tr>
<tr>
<td>HbC</td>
<td>6</td>
<td>Glutamic acid → Lysine</td>
</tr>
<tr>
<td>HbE</td>
<td>26</td>
<td>Glutamic acid → Lysine</td>
</tr>
<tr>
<td>γ Chain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbF</td>
<td>6</td>
<td>Glutamic acid → Lysine</td>
</tr>
</tbody>
</table>

**Table 1.** Commonly Encountered Qualitative Hemoglobin Variants
deficiency affects the hemoglobin of both fetuses and adults. Lack of α-chain production altogether is incompatible with life, and affected fetuses are typically stillborn (hydrops fetalis).

The types of β-thalassemia are classified according to their zygosity as either minor (heterozygous) or major (homozygous). The disease commonly is secondary to point mutations that lead to impaired or absent β-chain synthesis. Mutations that result in complete suppression of the β chain are designated as β0, whereas mutations that result in diminished synthesis are designated as β+.

Other thalassemia subtypes are δ and δβ. δ-Thalassemia is characterized by output of a diminished number of δ chains, whereas δβ is associated with suppression of β- and δ-chain synthesis. Rare forms such as homozygous εγδβ-thalassemia are incompatible with life, and such mutations have only been observed in heterozygotes.

Variants that present with combined qualitative and quantitative hemoglobin abnormalities are also seen, the most common being sickle/β-thalassemia. The combination of both underlying abnormalities in one genotype is named compound hemoglobin. Table 3 presents a functional overview of the most common quantitative and compound disorders.

### EPIDEMIOLOGY

Hemoglobinopathies have historically clustered in geographical areas in which malaria is endemic. The assumption is that the HbS mutation conferred a selective advantage for heterozygotes. Homozygotes may die of their disease, whereas hemoglobin A/A individuals are more apt to die of malaria. The most genetically fit person in the malaria belt population is the heterozygote. It is estimated that approximately 7% of the world population carries a globin-gene mutation, most frequently inherited as an autosomal recessive trait.

Thalassemias are the most common genetic disorders worldwide. Approximately 15% of African Americans are silent carriers for α-thalassemia; the α-thalassemia trait occurs in 3% of the African-American population and in 1% to 15% of persons of Mediterranean origin. β-Thalassemia is prevalent in Mediterranean populations (10%–15% incidence), as well as those from Southeast Asia, West Africa, and the Middle East. It occurs in less than 1% of African Americans.

HbS, HbC, and hemoglobin E (HbE) are the most frequently encountered qualitative hemoglobinopathies. HbS has the greatest prevalence in tropical Africa, with a heterozygous frequency up to 20%. The sickle cell gene has also been reported in the Middle East, Greece, and India, although it occurs in these countries at a markedly lower rate. In the United States, HbS has been reported in 9% of the African-American population. HbC is found in more than 30% of the West African population and has been reported in approximately 3% of African Americans. HbE is found predominantly in Southeast Asia, most commonly in Thailand and Cambodia and less commonly in Malaysia.

Through migration, hemoglobinopathies have spread from their native areas and are now endemic throughout Europe, the Americas, and Australia. Although rare, thalassemias can occur in all racial groups due to sporadic mutations; thus, racial background does not preclude the diagnosis.

### CASE PRESENTATION

A 21-year-old man presents to the emergency department with chest pain that started 12 hours ago. He has a diagnosis of HbS/β0 thalassemia. His outpatient medications are hydroxyurea, folate, and oxytocin as needed for pain.

His past medical history is significant for a splenectomy at the age of 5 years, a cholecystectomy at age 8 years, and avascular necrosis of the left femoral head. He also has mild cardiac dysfunction with global left ventricular hypokinesis and an ejection fraction of 50% by recent echocardiography. His last hospitalization was for a pain crisis that occurred 2 years ago.

The patient has no history of smoking, alcohol use, or drug abuse; he is currently enrolled in college and
he describes himself as single. His mother is originally from Iran; his father was born in West Africa.

On further questioning, the patient complains of diffuse throbbing chest pain that he ranks as 8/10 on a pain scale. He reports the pain is mostly anterior chest pain and states that his usual sickle cell pain is lower back and joint pain and is relieved by nonsteroidal anti-inflammatory agents. He is afebrile with a pulse of 108 bpm, blood pressure of 135/67 mm Hg, respiratory rate of 21 breaths/min, and an oxygen saturation of 93% on room air.

It is apparent that the patient is in some degree of physical distress, using accessory muscles to breath. His pulmonary exam is significant for crackles at the base of his right lobe. On cardiac auscultation he has a grade III systolic murmur over his right upper sternal border. The remainder of his physical examination is unremarkable.

Results of initial laboratory tests show a white blood cell (WBC) count of 18,100/μL, with a neutrophilia; a hemoglobin level of 7.3 g/dL, down from his baseline of 9 g/dL; a mean corpuscular volume (MCV) of 77 fL, (normal, 80–96 fL); and a platelet count of 424,000/μL (normal, 150,000–400,000/μL). A peripheral blood smear shows microcytosis and polychromatophilia. The patient’s urinalysis is normal; blood cultures are negative for bacteria after 48 hours. A chest radiograph shows right basilar opacities.

**CLINICAL PRESENTATION**

How a patient presents depends on the characteristics of the underlying hemoglobinopathy. Mutations or alterations of the globin protein produce pronounced changes in the functional property of hemoglobin, including oxygen affinity and solubility, and impair the structural integrity of the erythrocyte. Heterozygous disorders usually have a benign presentation, whereas homozygous disorders can lead to significant anemia and hemolytic and/or vaso-occlusive crises. Qualitative hemoglobinopathies (eg, homozygous HbS) are characterized by rigid red blood cells that do not pass through capillaries and cause microinfarction or vaso-occlusion, both of which can lead to acute and chronic organ damage. The amount of sickle cells is directly related to the severity of the hemolytic process. That said, sickle cell disease remains a highly phenotypically variable disease. In the steady state, individuals with a qualitative hemoglobinopathy usually present with a normochromic, normocytic anemia in the range of 5 to 11 g/dL. The anemia is usually accompanied by an elevated reticulocyte count and a reduced erythropoietin level relative to the anemia. Laboratory workup is indicative of hemolysis, as indirect serum bilirubin and lactate dehydrogenase (LDH) are elevated.

Current risk stratification for common complications remains incomplete, but certain findings are predictive of outcomes. For example, a low HbF concentration and leukocytosis are associated with increased risk of early death, acute chest syndrome, and painful crises. Higher steady state hemoglobin concentrations are associated with increased risk of early death, acute chest syndrome, and painful crises. By contrast, patients with sickle cell/β-thalassemia have more irreversible sickled cells in the peripheral smear than patients with sickle cell/β+. Both compound sickle cell variants present with clinical manifestations, although they are less severe than those seen with homozygous HbS.

Quantitative and qualitative hemoglobinopathies can present with a similar range of anemia. The majority of patients with α- and β-thalassemia minor are diagnosed because of an asymptomatic microcytic, hypochromic anemia. Anemia can be more pronounced.

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**Table 3. Functional Classification of Quantitative and Combined Hemoglobinopathies**

<table>
<thead>
<tr>
<th>Quantitative Disorders (Thalassemia)</th>
<th>Globulin Aﬀected Clinical Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Thalassemia</td>
<td>Decreased α chains</td>
</tr>
<tr>
<td>Normal (100% globulin output)</td>
<td>4: aα/aα</td>
</tr>
<tr>
<td>Silent carrier, 75%</td>
<td>3: -aα/aα</td>
</tr>
<tr>
<td>α-Thalassemia trait, 50%</td>
<td>2: 0α or -aα</td>
</tr>
<tr>
<td>HbH disease, 25%</td>
<td>1: -aα</td>
</tr>
<tr>
<td>Hydrops fetalis, 0%</td>
<td>0: —/—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combined Disorders</th>
<th>β Globin Genotype</th>
<th>Clinical Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle/β0-thalassemia</td>
<td>S-β0</td>
<td>Moderate to severe hemolysis; overlaps with SS in severity</td>
</tr>
<tr>
<td>Sickle/β+ thalassemia</td>
<td>S-β+</td>
<td>Mild hemolysis</td>
</tr>
</tbody>
</table>

- = absent or deleted α chain; — = both genes on the locus deleted; HbH = hemoglobin H; SS = sickle cell disease.
in thalassemias of intermediate degree, while in thalassemia major patients present with life-long transfusion-dependent anemia and iron overload syndromes, which untreated can lead to end organ damage.

**Organ-Specific Findings**

The function of blood and its role in oxygen delivery means that hemoglobinopathies can affect any organ system. Organ findings in hemoglobinopathy reflect the effects of compensatory hemoglobin production, distribution and disposal of hemolized red blood cells, and iron deposition, particularly from recurrent transfusions. The most commonly affected organ systems are the cardiopulmonary, renal, and central nervous systems, skin, bone, and the genitourinary, endocrine and the reticuloendothelial systems (Table 4).

**Cardiopulmonary** symptoms of shortness of breath and tachycardia secondary to anemia are the most common presenting symptoms of sickle cell disease.\(^{17}\) Chronic tachycardias can result in ventricular remodeling. In HbS disease, recurrent occlusive crises of the cardiac and pulmonary vasculature result in micro-infarcts that eventually alter blood supply, cardiac workload, and cardiac contractility.\(^{18-20}\) Fat embolus from bone infarctions can lead to pulmonary emboli and subsequent changes in pulmonary resistance. As the disease progresses, cor pulmonale with fatal arrhythmias can result.\(^{21}\) In severe hemoglobinopathies, particularly thalassemia major, frequent transfusions can result in a restrictive cardiomyopathy due to iron deposition within the myocardium.\(^{22}\)

**Renal.** Papillary necrosis due to chronic microinfarction of the renal papilla presents as isosthenuria—an inability to concentrate or dilute the urine, resulting in a constant altered osmolality.\(^{23}\) More than half of sickle cell patients will have enlarged kidneys on radiological exam. Progressive renal destruction eventually necessitates dialysis. An association between medullary renal cell neoplasms and sickle cell disease has also been postulated.\(^{24}\)

**Central nervous system** injuries can range from silent cerebral infarcts in children\(^{16}\) to life-threatening major occlusion of the anterior or middle cerebral arteries in sickle cell disease. Silent strokes are the most common form of neurologic injury. Risk of stroke increases with low baseline hemoglobin, increased homocysteine levels, HLA polymorphisms, large vessel inflammation (unknown pathophysiology),\(^{25}\) previous transient ischemic attacks, and priapism.\(^{26}\) Occlusion can extend to the retinal vessels, resulting in hemorrhage, neovascularization (proliferative and nonproliferative retinopathy), scarring, retinal detachment, and even blindness.\(^{27}\)

**Bone.** Bone, the production powerhouse of the erythrocyte, can be significantly affected in hemoglobinopathies. From early childhood, normal bone growth and development can be interrupted: medullary spaces widen as a result of chronic erythroblast hyperplasia and destruction; thinned cortices and sparse trabecular patterns can be seen;\(^{28}\) vertebral bodies may show biconcavities; and a chondrolytic arthritis can develop at sites of joint space narrowing. Magnetic resonance imaging findings show extensive fibrotic scarring of the marrow cavity of long bones. Persons with thalassemia develop marked skeletal abnormalities, particularly of the skull (frontal bossing) and facial bones (“chipmunk” facies from maxillary marrow hyperplasia). In sickle cell patients, avascular necrosis

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**Table 4. Organ-Specific Findings in Hemoglobinopathies**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Abnormalities</th>
<th>Hgb Level, g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell trait</td>
<td>None; rare painless hematuria</td>
<td>Normal</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>Vaso-occlusive crises with infarction of spleen, brain, marrow, kidney, lung; aseptic necrosis of bone; gallstones; priapism; ankle ulcers</td>
<td>7–10</td>
</tr>
<tr>
<td>S/S0 thalassemia</td>
<td>Same as sickle cell anemia</td>
<td>7–10</td>
</tr>
<tr>
<td>S/S+ thalassemia</td>
<td>Same as sickle cell anemia</td>
<td>10–14</td>
</tr>
<tr>
<td>HbSC</td>
<td>Rare crises and aseptic necrosis; painless hematuria</td>
<td>10–14</td>
</tr>
<tr>
<td>Silent thalassemia: —/αα</td>
<td>Minimal microcytosis</td>
<td>15</td>
</tr>
<tr>
<td>Thalassemia trait: α/-α (homozygous α-thal-2) or —/α heterozygous (α-thal-1)</td>
<td>Similar to β-thalassemia minor; mild anemia; rare blood cell inclusions (precipitated HbH)</td>
<td>12–13</td>
</tr>
<tr>
<td>HbH disease: —/-α (heterozygous α-thal-1/α-thal-2)</td>
<td>Thalassemia intermedia with moderately severe hemolytic anemia; precipitated HbH; transfusions necessary in midlife</td>
<td>6–10</td>
</tr>
<tr>
<td>Hydrops fetalis: —/- — homozygous α-thal-1</td>
<td>Tissue asphyxia, congestive heart failure, edema</td>
<td>Fatal in utero or at birth</td>
</tr>
</tbody>
</table>

- = absent or deleted α chain; — = both genes on the locus deleted.
of the bone commonly occurs in the femoral/humeral heads; in infants under the age of 9 months, avascular necrosis can manifest as dactylitis. However, the entire skeleton is at risk of infarction; in the most dramatic presentation of bone involvement, the anterior tibia can become swollen, tender, and erythematous. Necrotic marrow presents risks of superinfection from encapsulated organisms (ie, Salmonella and Staphylococcus) and embolus to the lung, causing acute chest syndrome or sudden death.

**Reticuloendothelial system.** Increased red cell destruction in childhood leads to alterations in the reticuloendothelial system that manifest initially as splenomegaly, resultant extramedullary hematopoiesis, and eventual autosplenectomy, often between 18 and 36 months of age, with subsequent immunocompromise. Patients are particularly vulnerable to infections with encapsulated organisms. Splenomegaly presents with symptoms of early satiety and laboratory values consistent with hypersplenism. In thalassemic disease, constant destruction of globin chains can lead to spleen “work hypertrophy” and a resultant hypersplenism, plasma volume expansion, and erythroid marrow expansion with worsening anemia.

The destruction of dysfunctional cells in the spleen and liver can present with hepatosplenoemgal and jaundice. Between 50% and 60% of patients develop pigment gallstones, secondary to a hyperbilirubinemia; there is a low overall incidence of primary choledocholithiasis. The need for recurrent transfusions in many hemoglobinopathies leads to iron overload in the liver, fibrosis, and endstage liver disease.

Acute splenic sequestration (ASSC) is a life-threatening event in the sickle cell patient. Intrasplenic trapping of red blood cells can cause a precipitous fall in hemoglobin and resultant hypovolemia. ASSC can be defined by a decrease of at least 2 g/dL from a patient’s steady-state hemoglobin level with evidence of increased erythropoiesis (ie, increased reticulocyte level, enlarging spleen). Clinically, ASSC manifests with sudden weakness, pallor, tachycardia, tachypnea, and abdominal fullness.

**Endocrine** abnormalities can result from hormonal and structural disruptions due to disordered hematopoiesis as well as from recurrent transfusions and subsequent iron overload. Growth retardation, growth failure, dysfunctional sexual development, diabetes and hypothyroidism are often seen.

**Skin.** Ulcerations, particularly around the ankles, are common problems in sickle cell patients. The general immunocompromised state of many of these patients, often exacerbated by the use of the myelosuppressive medication hydroxyurea, predisposes ulcerations to infection. In addition, lower levels of hemoglobin seen in patients with skin ulcerations (and concomitant elevations in LDH, bilirubin, and aspartate aminotransferase) suggest that hemolysis occurs at greater intensity in this patient population; transfusion provides effective therapy.

**CASE CONTINUED**

The patient is diagnosed with acute chest syndrome and is admitted to the hospital for further management. A comprehensive metabolic panel reveals an elevated total bilirubin of 1.7 mg/dL (normal range, 0.3–1.2 mg/dL), a direct bilirubin of 0.7 mg/dL (normal range, 0.0–0.4 mg/dL), and an LDH of 404 U/L (normal range, 94–250 U/L). The remainder of the results, including liver and renal function, are normal; coagulation parameters are within normal limits. Iron studies are not sent due to the acuity of the event; blood is sent for typing and crossmatching.

The patient receives 5 mg of morphine intravenously in the ED and is then started on a morphine patient-controlled anesthesia pump (PCA) with settings of 1 mg/hr basal rate and an as-needed bolus. A bowel regimen with docusate and semia is started to prevent narcotic-induced constipation. He also receives an intravenous (IV) infusion of ketorolac, IV fluids at 125 mL/hour, and 2 units of packed red blood cells. Empiric IV antibiotic therapy is started for possible community-acquired pneumonia. He is continued on his outpatient hydroxyurea and folate.

**MEDICAL EMERGENCIES ASSOCIATED WITH HEMOGLOBINOPATHIES**

The diagnosis of a hemoglobinopathy is never an emergency. However, complications of hemoglobinopathies such as sepsis, thrombotic stroke (children), cerebral hemorrhage in adults with sickle cell anemia, rib infarction, acute chest syndrome (ACS)/acute respiratory distress syndrome, ASSC, severe aplasia, and fat embolism syndrome can all be considered emergencies.

**Pain Crises**

Pain and pain crises are the most common reasons for patients with hemoglobinopathies to be hospitalized; these crises can be potent indicators of serious organ dysfunction. Four different variants of crises are differentiated: vaso-occlusive, aplastic, sequestration, and hemolytic. Vaso-occlusive crises occur most frequently; the implicated pathophysiology of such episodes includes complex interactions between endothelium, activated plasma factors, leukocytes and, in the case of sickle cell disease, rigid, inflexible red blood cells. Obstruction of
the microvasculature compromises oxygen delivery to the organ. The type of vascular supply as well as the affected organ dramatically changes the acuteness of care.

**Vaso-occlusive Crises**

Vaso-occlusive crises that affect the central nervous system can have devastating complications. Cerebrovascular accidents in patients with a hemoglobinopathy are thought to occur due to existent inflammatory lesions in the major vessels (ie, the internal carotid arteries and the anterior and middle cerebral arteries), with most patients have no forewarning of an imminent stroke. The highest incidence of central nervous system crises is observed in children and adults older than 29 years of age. In approximately 25% of patients, prior painful or aplastic crises, transient ischemic attacks, human leukocyte antigen loci polymorphisms, low baseline hemoglobin, and an elevated diastolic blood pressure can signal a predisposition to stroke. Screening methods to identify disease before it causes extreme devastation are being investigated. In particular, the use of transcranial Doppler ultrasonography in high-risk patient populations to evaluate for flow-velocity changes is showing promise. Between 46% to 90% of patients who go untreated following an initial stroke will suffer a repeat stroke; the highest percentage of repeat strokes will occur within 30 months of the initial stroke. Exchange transfusion has been shown superior to simple transfusion both as acute treatment and in the prevention of a second stroke. If the use of hydroxyurea in patients with prior stroke leads to a significant increase in HbF, transfusions can be discontinued. In general, maintaining a HbS fraction less than 30% has also been shown to reduce the likelihood of stroke recurrence.

**Acute Chest Syndrome**

*Acute chest syndrome* is a general term for any condition that results in a new pulmonary infiltrate. The differential diagnosis is pneumonia, pulmonary embolism, and primary pulmonary thrombosis. ACS clinically presents as a combination of fever, chest pain, elevated white blood count, infection, and new pulmonary infiltrates. It is thought to occur secondary to the interplay of infection, infarction, and pulmonary embolus. In a study of 538 patients with ACS, only 38% of episodes had a clear defining pathophysiologic event. The incidence of ACS increases in the winter months and in children aged 2 to 4 years. The concentration of HbF and degree of anemia are inversely proportional to the incidence of ACS and directly proportional to the white blood cell count. Diagnostic criteria for ACS are as follows: new pulmonary infiltrate detected by chest radiograph involving at least one complete lung segment that is not consistent with the appearance of atelectasis and one or more of the following signs or symptoms:

- Chest pain
- Temperature > 38.5°C
- Tachypnea, wheezing, cough, or appearance of increased work of breathing
- Hypoxemia relative to baseline

In addition to general measures of hydration, pain control, oxygenation, and antibiotic treatment, if indicated, simple transfusion should be started and advanced to exchange transfusion or erythrocytapheresis if there is clinical progression, severe hypoxemia, multilobar disease, or previous history of severe ACS or cardiopulmonary disease. The goal of therapy is to decrease the HbS to less than 30% of total hemoglobin while not exceeding a hemoglobin level of 10 g/dL.

Rib infarction can also present with a form of acute chest pain—specifically pleuritis and splintering. If not treated promptly, it can result in acute respiratory distress syndrome requiring mechanical ventilation. Aggressive analgesia and use of incentive spirometry (10 puffs every 2 hours during daytime hours) can prevent 85% of the infiltrates that develop in patients having chest pain in the hospital.

**Priapism**

Low-flow priapism is a serious complication that occurs in approximately 35% of patients, usually before the age of 20 years. Sickling within the venous sinusoids during erection can lead to critical stasis, hypoxia, and acidemia. If left untreated, a patient can be rendered permanently impotent. Risk factors include prolonged sexual activity; fever; dehydration; and use of alcohol, marijuana, cocaine, psychotropic agents, phosphodiesterase-5 enzyme inhibitors, or exogenous testosterone. Diagnosis is made with color duplex Doppler ultrasonography or cavernosal blood gas measurement. Neither simple nor exchange transfusion has been found beneficial in treatment of acute priapism. In erections lasting longer than 2 hours, aspiration of blood from the corpus cavernosum followed by a saline or adrenergic agonist infusion is standard treatment. In severe cases, surgical procedures, such as Winter’s procedure, shunt blood away from the corpus cavernosum to the more pliable corpus spongiosum.

**Thalassemia-Specific Emergencies**

Emergencies in thalassemias largely correlate with the acuity of the anemia. In β-thalassemia major, critical changes are seen in infants after 6 months of age, when hemoglobin production changes from fetal to adult
hemoglobin. Infants develop chronic anemia, with stigmata of profound hemolysis. Developmental delays, growth retardation, and abdominal swelling with enlargement of the liver and spleen, as well as consequent jaundice reflect the onset of severe hemolytic anemia. Around 80% of untreated children die within the first years of life, due to consequences of severe anemia, high-output heart failure, and susceptibility to infection.

**CASE RESOLUTION**

Initially, the patient’s pain does not improve, so the basal rate of his morphine PCA is increased to 2 mg/hr. Repeat blood work after 16 hours reveals a hemoglobin level of 9.2 mg/dL, with a WBC of 16,200/μL and platelet count of 414,000/μL. The HbF level on admission is 4.7% (normal range, 0.0%–1.5%). The peripheral smear reveals an average of 2 sickled cells per high-power field, with microcytic cells and polychromasia. After 48 hours of PCA treatment, the pain medication is switched to oral oxycodeone. He has no desaturation or fevers over 72 hours; his vital signs normalize and he is switched to an oral antibiotic regimen. A repeat chest radiograph reveals a decrease in the right basal opacity. After 120 hours, the patient’s vital signs remain stable, he is asymptomatic, and is discharged on as-needed pain regimen and 5 more days of oral antibiotics. He is scheduled for a follow-up appointment at the Sickle Cell Hematology clinic.

**DIAGNOSIS**

Diagnostic recommendations regarding the laboratory investigation of abnormal hemoglobins were first made in 1975 by the International Committee for Standardization in Hematology expert panel. The recommend initial testing included a complete blood count, electrophoresis at pH 9.2, tests for solubility, and quantification of HbA2 and HbF. The identification of an abnormal hemoglobin required further testing, using additional techniques such as electrophoresis at pH 6.0 to 6.2, globin chain separation, and isoelectric focusing. Heat and isopropanol stability tests were recommended for detection of unstable hemoglobin or hemoglobin with altered oxygen affinity. Although electrophoresis at alkaline and acid pH has been widely used for many years, cation-exchange high-performance liquid chromatography, or HPLC, has become the method of choice for the quantitation of HbA2 and HbF and identification of hemoglobin variants. HPLC has streamlined the recommended preliminary and follow-up tests for the identification of hemoglobinopathies, providing a rapid and complete diagnostic work-up in a majority of cases. Although not usually indicated, bone marrow biopsy will demonstrate marrow erythroid hyperplasia and a prominent increase in iron. Flow cytometry is used to detect and quantify HbF. Definite diagnosis of a hemoglobin variant may require mutational analysis of a specific globin gene by polymerase chain reaction or electrophoresis gene analysis by Southern blot. Detailed structural analysis of the globin chains is done by fingerprinting of cryptic digests by electrophoresis, amino acid sequencing, and nucleic acid mutation analysis. Genetic testing is recommended in infants, as hemoglobin electrophoresis will be altered by a predominance of HbF. Genetic counseling is being used in couples with significant history to prevent severe forms of thalassemia. Extraction of fetal DNA either by amniotic fluid aspiration or chorionic villus sampling enables diagnosis of hemoglobin disorders in utero. Polymerase chain reaction combined with the use of oligonucleotide probes aids in fast and reliable diagnosis of mutations.

**TREATMENT**

**Qualitative Hemoglobinopathies**

The underlying pathophysiology of hemoglobinopathies is, with exceptions, an inherited stem cell defect. In most cases, treatment of qualitative hemoglobinopathies entails symptomatic management, whereas only a fraction of patients undergo curative-intent stem cell transplantation. Emphasis in supportive care is directed towards hydration, oxygenation, transfusion, and treatment or prevention of infection, as dehydration, low oxygen saturation, high proportion of HbS, and infection can trigger a sickle cell crisis. Administration of Haemophilus influenzae and pneumococcal vaccines is recommended, especially in children younger than 5 years. Prophylactic transfusions have been shown to decrease the frequency of vaso-occlusive crises. A downside of frequent transfusions is the increased risk of developing red blood cell alloantibodies. Therefore, in this patient population, it is important to transfuse leukoreduced and C, E, K1 antigen–matched blood. If surgical procedures are planned, patients at risk for crises should have a HbS level lower than 30%, which can be achieved through simple or exchange transfusion. Studies suggest that patients undergoing surgery with general anesthetics can be preoperatively treated with simple transfusions to hemoglobin levels of about 10 g/dL rather than with aggressive exchange transfusions. The effectiveness of simple versus exchange transfusion, even in the setting of an acute vaso-occlusive crises, remains uncertain due to lack of randomized clinical trials. Patients with frequent transfusions have to be monitored for iron overload syndrome and, if indicated, started on chelation therapy. Folic acid supplementation is commonly
Contraindication

Concerns about carcinogenesis and toxicity. Sickle cell levels, but it has never achieved widespread use due to important in patients taking hydroxyurea.

Indications and contraindications for treatment with hydroxyurea are listed in Table 5.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Contraindication</th>
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<tbody>
<tr>
<td>&gt; 3 pain crises in 1 year</td>
<td>Patients (female) unwilling to use contraception.</td>
</tr>
<tr>
<td>Persistent occurrences of priapism</td>
<td>Receiving large numbers of narcotics regularly.</td>
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<tr>
<td>despite standard therapy</td>
<td></td>
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<tr>
<td>Creatinine levels &lt; 1.7 mg</td>
<td>Active liver disease</td>
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<tr>
<td>Average reticulocyte count &gt; 150,000</td>
<td>Positive HIV test without special informed consent.</td>
</tr>
<tr>
<td>Symptomatic anemia with alloimmunization</td>
<td>Recent cerebrovascular accident</td>
</tr>
<tr>
<td></td>
<td>History of noncompliance</td>
</tr>
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</table>


used to support rapid cell regeneration, but there is little evidence of clinical benefit, except for patients who are pregnant or folate deficient.

HbF protects red cells from sickling, although no significant correlation exists between the HbF level and the severity of clinical manifestation. Hydroxyurea is clinically used either alone or in combination with erythropoietin to increase the amount of HbF; it has been shown to reduce the frequency of painful crises and blood transfusion and may improve overall survival. The response to hydroxyurea is more robust in infants and children up to adolescence than in adults. It is the only drug approved by the US Food and Drug Administration to treat sickle cell anemia. Indications and contraindications for treatment with hydroxyurea are in Table 5.

The recommended dosing procedure for hydroxyurea is to administer 15 mg/kg (usually 1000 mg in adults) and check the complete blood count every 2 weeks to avoid severe leukopenia or thrombocytopenia. Every 6 weeks the dose is increased by 5 mg/kg (usually 500 mg in adults) until the absolute neutrophil count rather than the total WBC count is approximate 1000/μL. When the patient is titered to a neutrophil count of 1000/μL, then the complete blood count can be checked every 3 months. Toxicity develops below 500/μL. Discussion of contraceptive precautions is important in patients taking hydroxyurea.

5-Azaacytidine has also been found to elevate HbF levels, but it has never achieved widespread use due to concerns about carcinogenesis and toxicity. Sickle cell trait, HbC, and hemoglobin D usually have an excellent prognosis and need no specific treatment.

**Thalassemia**

Treatment for thalassemia is curative only with bone marrow transplantation. Symptomatic management for nontransplanted individuals entails blood transfusion, management of iron stores, and generalized medical care. As in sickle cell disease, patients are at risk for infections, especially after developing skull deformities in the ENT area. Infections due to the compromised immune system should be treated empirically. The skull deformities also lead to an increase in structural dental problems. Surveillance for alloimmunization and hepatitis C, hepatitis B and HIV infection should be done routinely in recipients of frequent blood transfusion. Splenectomy should only be performed in patients with sudden increased transfusion requirements or pain secondary to splenomegaly. The risk of splenectomy is susceptibility for overwhelming pneumococcal infections and thromboembolic events. Other unstable hemoglobin variants exist, and these are usually treated symptomatically with transfusion, hydration, and oxygenation. All patients with thalassemia variants that require frequent transfusion need surveillance of the iron stores and chelation therapy, if indicated. Indications for start of chelation therapy in chronic transfusion-dependent thalassemias are ferritin levels greater than 1000 mg and/or signs of iron overload.

**Bone Marrow Transplantation**

Hematopoietic stem cell transplantation (HSCT) remains the only curative option for hemoglobinopathies available. Use of HSCT in thalassemia was first described in 1982. Candidates considered for transplants are usually children with poor prognosis. The best results are obtained in patients with HLA-matched siblings. Hepatomegaly, hepatic fibrosis, and quality of chelation therapy have been identified as significant outcome variables in β-thalassemia transplant candidates. Long-term survival after transplantation averages approximately 80%, and 85% to 90% of patients are cured. Data on HSCT for sickle cell disease is not as extensive due to the variable course of disease and prognostic factors predicting severity of symptoms. Eligibility for transplant is limited because of advanced stage disease or missing HLA matches. The role for early transplantation in presymptomatic young children has yet to be defined. Nonmyeloablative regimens have been tried to reduce toxicity, although graft rejection or disease recurrence was seen.
INVESTIGATIONAL THERAPIES

Cell receptors and ion pump channels have been targeted to control hemolysis in sickle cell disease. Oral magnesium has been studied as an inhibitor of the KCL co-transporter, with insufficient data supporting a benefit. Anti-adherence therapy targeting erythrocyte-endothelial-leukocytes and platelets has been studied without any current clinical approved therapies. Nitric oxide, a potent vasodilator, has been used in the treatment of acute sickle cell disease and found to reduce the pain score and pain medication use in children.73

In thalassemia, peripheral stem cell transplant as opposed to HSCT has been studied. Compared to bone marrow transplantation, it has a shorter engraftment time but a higher incidence of graft-versus-host disease.74 In view of the low incidence of graft-versus-host disease associated with allogenic cord blood transplantation (CBT), this procedure is particularly appealing. Available evidence indicates that related donor CBT is a safe and effective option for patients with hemoglobinopathies, offering results at least as good as those reported using bone marrow cells.75 Hematopoietic stem cell–targeted gene transfer is currently being investigated as a treatment option for hemoglobinopathies caused by single gene defects.76

OUTCOMES AND PROGNOSIS

Transfusion and chelation treatment have improved outcomes in severe forms of β-thalassemia. Patients with an estimated serum ferritin level below 500 ng/mL over a period of 12 years were found to have a disease-free survival rate of 91%.77 Transplantation is able to cure patients and has become a standard procedure. In milder forms of thalassemia, judicious use of splenectomy in patients with hypersplenism, vaccination, and a good standard of general care have an impact on survival. Prevention through screening and genetic counseling remains essential to prevent severe forms of thalassemia.

Survival in sickle cell disease patients is overall reduced but has been steadily improving. With good medical care, patients with sickle cell disease survive to middle age.77 Over the last few decades, mortality has especially dropped in children. Survival has improved due to newborn screening programs, penicillin prophylaxis of disease caused by Streptococcus pneumoniae, and perhaps pneumococcal vaccine. The most common cause of death in sickle cell disease is infection, and others are pulmonary emboli, stroke, and splenic sequestration. Neither sickle cell trait nor HbC appear to impact survival. Genetic counseling also is important to prevent severe disease and disease side effects. Patients at high risk for sickle cell disease have the option of transplantation.

CONCLUSION

Hemoglobinopathies are hemopoietic stem cell disorders with qualitative, quantitative, and combined globin chain abnormalities. The range of newly diagnosed genotypes with resulting phenotype has been steadily increasing due to improved laboratory diagnostic procedures. Treatment remains supportive in the majority of encountered diseases. Curative treatment in high-risk patients is limited to HSCT. Transplantation has significant risks but has become standard procedure, more so in thalassemias than in sickle cell disease, due to improved peri- and posttransplantation care. Genetic counseling and screening are relevant in predicting and diagnosing clinical significant genotypes. Further studies are needed to expedite curative treatment options and prevent recurrent crises and long-term side effects.

REFERENCES


