

Sickle Cell Disease

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Dr Driscoll did not
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Objectives After completing this article, readers should be able to:

1. Describe the pathogenesis of sickle cell disease.
2. Delineate the complications of sickle cell disease and their management.
3. Review guidelines for health maintenance and preventive measures.
4. Discuss the current treatments for sickle cell disease.

Introduction

Sickle cell disease (SCD) is a chronic hemolytic anemia that includes the hemoglobin (Hb) variants SS, SC, S-beta thalassemia, SO Arab, SD, and other rare S-Hb genotypes. SCD is one of the most common genetic diseases worldwide. Sickle disorders are seen commonly in sub-Saharan Africa but also occur in the Mediterranean, India, and the Arabian Peninsula. The geographic distribution of sickle hemoglobinopathies corresponds to the distribution of malaria; indeed, the sickle gene in the heterozygote (AS) form protects against death from endemic *Plasmodium falciparum* malaria infection. In addition, the clinical manifestations of SCD vary among these geographic sites, with individuals from India, the Arabian Peninsula, and Senegal having milder disease than those from parts of Africa. This pattern suggests that genetic modifiers ameliorate the disease in certain populations and contribute to the significant variation in clinical manifestations. The presence of SCD in North, South, and Central America is due to immigration patterns and represents primarily the more severe African types.

Pathogenesis

The genetic defect producing sickle Hb is a single nucleotide substitution (GTG for GAG) at codon 6 of the beta globin gene on chromosome 11 that results in the substitution of valine for glutamic acid. This hydrophobic amino acid substitution allows Hb S to polymerize on deoxygenation, and multiple polymers bundle to form rodlike structures that distort the red cell into the classic crescent shape. Sickled red cells are less deformable in the microcirculation and provoke a cascade of events that results in vascular occlusion, organ ischemia, and eventually, chronic end-organ damage. The ancillary events of polymerization that contribute to red cell sickling include erythrocyte dehydration due to cation efflux, erythrocyte and leukocyte adhesion to an activated endothelium, abnormal vasomotor tone favoring vasoconstriction, and hypercoagulability.

Diagnosis

SCD can be diagnosed in the laboratory by isoelectric focusing (IEF), hemoglobin electrophoresis (HbEp), high-performance liquid chromatography (HPLC), or DNA analysis (Table 1). Newborn screening programs in 44 states and the District of Columbia include testing for Hb disorders and rely primarily on a combination of IEF, HbEp, and HPLC, which have a range in sensitivity of 93.1% to 100% and a specificity of 99.9% to 100%. Newborn screening allows the early identification of affected infants, leading to intervention with prophylactic penicillin no later than 3 months of age and parental education. Such early intervention has decreased the deaths from pneumococcal infection in young children who have SCD. In states where Hb disorders are not included in the newborn screen due to a small at-risk population, physicians who see infants at high risk for SCD, based on ethnicity, should test for the disease by HbEp prior to 3 months of age.

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Table 1. Laboratory Values in Sickle Cell Syndromes Among Those Older Than 5 Years

Hemoglobin (Hb) Variant	Hb ¹ Electrophoresis	Hb (g/dL)	MCV ²	Hb S (%)	Hb A (%)	Hb A ₂ (%)	Hb F (%)
Hb-SS	SF	6 to 8	Normal or ↑ ³	>90	0	<3.5	<10
Hb-S-beta ⁰ thalassemia	SF	7 to 9	↓	>80	0	>3.5	<20
Hb-S-beta ⁺ thalassemia	SAF	9 to 12	↓	>60	5 to 30	>3.5	<20
Hb-SC ⁴	SCF	10 to 14	Normal or ↓	50	0	NA ⁵	<2
Hb-SHPPFH	SF	11 to 14	Normal or ↓	60	0	<2.5	35 to 40

¹Hemoglobins are reported in order of quantity.
²MCV=mean cell volume.
³Hb-SS with coexisting alpha thalassemia may have decreased MCV and increased A₂.
⁴Hb C: measures ~50%.
⁵Hb A₂ not measurable in the presence of Hb C.

Screening tests such as the Sickledex[®] (Ortho-McNeil Pharmaceutical Corporation, Raritan, NJ) are inappropriate in the newborn because results are negative in the presence of a large quantity of fetal Hb. In the United States, the prevalence of SCD among African-Americans is 1 in 375 births and among Hispanics is 1 in 1,200 births. It is expected that these numbers will increase with increased immigration patterns, especially from Africa where the sickle carrier (AS) prevalence of 15% to 25% is higher than the 9% seen in the United States.

Infants in whom SCD is diagnosed should be referred to a pediatric hematologist by 3 months of age. In areas where pediatric hematology consultation is not available, the pediatrician can be guided by the health maintenance guidelines in Table 2 and by phone consultation with an expert at any of the National Institutes of Health (NIH) Comprehensive Sickle Cell Disease Centers (www.sicklecell-info.org). Infants who have a hemoglobinopathy trait (Hb-AS, -AC, -A-beta thalassemia) do not need referral to a pediatric hematologist. However, the parents of a child who has a trait could be at risk for having a child who has SCD or thalassemia and, therefore, should have their Hb status confirmed by HbEp and be referred to a genetic counselor if indicated.

Prenatal diagnosis of Hb disorders by mutation-specific DNA methods has been available for 20 years and is accomplished by chorionic villus biopsy in the first trimester and by amniocentesis in the second trimester. However, there is less acceptance of termination of an affected pregnancy among parents at risk for a child who has SCD than those at risk for thalassemia. This difference may be due, in part, to the significant clinical variation among children who have SCD and the current inability to predict precisely the clinical course of a child who has SCD compared with the better defined clinical

course of the transfusion-dependent thalassemia syndromes. Preimplantation genetic diagnosis also is available for sickle cell disease. This methodology involves DNA diagnosis of in vitro fertilized embryos at the blastocyst stage prior to implantation and, therefore, can select for embryos not affected with SCD.

Clinical Manifestations

The clinical manifestations of SCD appear during the first postnatal year as fetal Hb concentrations decline. Fetal Hb is protective because it inhibits deoxy-Hb S polymerization in the red blood cell. The rare individuals who have genetic mutations leading to persistence of fetal Hb production (Hb F >30%) have mild or no sickle cell symptoms. In addition, within the broad category of SCD, severity varies based on the Hb variant (SS>S-beta⁰ thalassemia>SC>S-beta⁺ thalassemia).

The clinical complications of SCD vary according to age (Table 3). Young children who have SCD are at increased risk for bacterial infection, splenic sequestration, and stroke; adolescents and adults begin to experience end-organ damage such as pulmonary hypertension, renal disease, stroke, avascular necrosis, leg ulcers, and chronic pain syndromes.

Today, the life expectancy for patients who have Hb-SS has increased to a median of 45 years and for Hb-SC patients to 65 years, a significant improvement over the median survival to age 14.3 years for patients having Hb-SS 3 decades ago. The improvement in life expectancy is related, in part, to early identification and prevention of death from pneumococcal sepsis in young children and to improved education regarding SCD complications and early intervention.

Table 2. Health Maintenance in Sickle Cell Disease

Age	Visits	Laboratory Studies	Medication	Immunization	Screening
Birth to 6 mo	q 2 mo	<ul style="list-style-type: none"> CBC, retic¹ HbEp² G₆PD³ 	<ul style="list-style-type: none"> Penicillin VK 125 mg BID (start by 3 mo) 	<ul style="list-style-type: none"> Heptavalent conjugated pneumococcal vaccine at 2, 4, and 6 mo 	
6 mo to 2 y	q 3 to 6 mo	<ul style="list-style-type: none"> CBC, retic HbEp repeat at 1 y BCP⁴ Iron/Ferritin 	<ul style="list-style-type: none"> Continue penicillin VK Folic acid 1 mg (start by 1 y) 	<ul style="list-style-type: none"> Influenza q year 	
2 to 5 y	q 6 mo	<ul style="list-style-type: none"> CBC, retic BCP Iron/Ferritin UA⁵ 	<ul style="list-style-type: none"> Change penicillin VK dose to 250 mg BID at 3 y Folic acid 	<ul style="list-style-type: none"> Pneumococcal 23-valent vaccine at 2 y and a booster at 5 y 	<ul style="list-style-type: none"> TCD⁶ at 2 y and q year to age 16 y Dentist
> 5 y	q 6 to 12 mo	<ul style="list-style-type: none"> CBC, retic BCP Iron/Ferritin UA 	<ul style="list-style-type: none"> Discontinue penicillin VK Folic acid 	<ul style="list-style-type: none"> Influenza q year 	<ul style="list-style-type: none"> TCD Retinal examination⁷ at 8 y and q yr Hip radiographs⁸ at 10 y and q yr Echo⁹ at 10 y and q 2 yr Dentist

¹CBC, retic= Complete blood count and reticulocyte count at each visit.

²HbEp= hemoglobin electrophoresis at first visit and repeat at 1 y of age.

³G₆PD= glucose-6-phosphate dehydrogenase at first visit.

⁴BCP= biochemical profile (blood urea nitrogen, creatinine, liver function tests) and iron/ferritin once a year.

⁵UA=urinalysis once a year.

⁶TCD=transcranial Doppler once a year at ages 2 to 16 y in those who have Hb SS and S-beta⁰ thalassemia.

⁷Retinal examination for sickle retinopathy at age 8 y and every year.

⁸Hips radiographs at age 10 y and every year for avascular necrosis.

⁹Echocardiography for pulmonary artery pressures at age 10 y and every 2 y.

Table 3. Clinical Features of Sickle Cell Disease

Complication	Features
Infection <ul style="list-style-type: none"> • <i>Streptococcus pneumoniae</i> sepsis • Osteomyelitis • Parvovirus B19 	Children <5 y of age <i>Salmonella</i> , <i>Staphylococcus aureus</i> Aplastic crises
Splenic Sequestration	Hb-SS <3 y; Hb-SC, S-beta thalassemia any age
Pulmonary Features <ul style="list-style-type: none"> • Acute chest syndrome • Pulmonary hypertension 	50% of patients 30% of adults who have Hb-SS
Neurologic Features <ul style="list-style-type: none"> • Overt stroke • Silent infarction on magnetic resonance imaging 	11% of Hb-SS children by 20 y 22% of Hb-SS children
Osteonecrosis <ul style="list-style-type: none"> • Femoral or humeral heads 	50% of Hb-SS (↑ with alpha thalassemia); 60% of Hb-SC
Retinopathy	50% of Hb-SC adults
Renal Insufficiency	5% to 20% of Hb-SS adults
Cholelithiasis	42% by adolescence
Leg Ulcers	10% to 25% of Hb-SS adults
Priapism	10% to 40% of Hb-SS males
Vaso-occlusive Pain Crisis	70% of all patients; 5% (Hb-SS) account for 30% of admissions

Infection

The spleen is the first organ damaged by sickling in the microcirculation. By 1 year of age, approximately 30% of patients who have Hb-SS have functional asplenia; by 6 years of age, 90% have functional asplenia. The risk of bacterial infection with encapsulated organisms is increased with splenic hypofunction or asplenia. The risk of bacteremia with *Streptococcus pneumoniae* is 400-fold higher in patients who have SCD. The use of prophylactic penicillin and immunization with the heptavalent-conjugated pneumococcal vaccine and the 23-valent pneumococcal polysaccharide vaccine has decreased the incidence of pneumococcal sepsis by 84% in children younger than 5 years of age. However, clinical guidelines for intervention with parenteral antibiotics in all children who have SCD and develop a temperature to at least 101°F (38.4°C) is mandated because there is a pattern of increasing resistance of *S pneumoniae* to penicillin and cephalosporins as well as incomplete protection of pneumococcal vaccines. Administration of a third-generation cephalosporin (ceftriaxone, cefotaxime) plus clindamycin or vancomycin for severe infections is the current practice. Outpatient management of fever in children who have SCD and low-risk parameters based on age, degree of fever, leukocyte count, clinical presentation, and parental compliance now is standard. Ceftriaxone is the antibiotic of choice for 48-hour outpatient therapy in such patients.

Osteomyelitis is another frequent infectious compli-

cation in SCD, with *Salmonella* sp isolated most commonly, followed by *Staphylococcus aureus*. The clinical presentation of osteomyelitis has significant overlap with vaso-occlusive (VOC) pain crises, which are far more common. No definitive imaging modalities (bone scan, magnetic resonance imaging) can differentiate with certainty between osteomyelitis and VOC. The diagnosis still relies on clinical assessment (fever, leukocytosis, erythrocyte sedimentation rate) or positive blood cultures from blood or bone obtained by aspiration.

Parvovirus B19, the most common cause of transient red cell aplasia, the so-called aplastic crises of SCD, has a predilection for young erythroblasts in bone marrow, which are plentiful in patients who have hemolytic anemias. Parvovirus B19 also is the cause of erythema infectiosum (fifth disease). In SCD, the infection usually is self-limited and may present with fever, upper respiratory tract symptoms, fatigue, pallor, an absence of scleral icterus, and a decrease from baseline Hb with reticulocytopenia. The reticulocytopenia may last 7 to 10 days, requiring transfusion in most cases for patients who have Hb-SS, but less often in those who have Hb-SC. Parvovirus in SCD also can be associated with more severe complications, such as bone marrow necrosis leading to pancytopenia, severe acute chest syndrome, stroke, and glomerulonephritis. During the convalescent period, however, reticulocytosis can be brisk, with pronounced anemia that can be mistaken for a hyperhemolytic event. The diagnosis can be confirmed by demonstrating in-

creased concentrations of parvovirus immunoglobulin M in blood. Protective immunity is lifelong, and the disease does not recur in patients who have SCD. Parvovirus is highly contagious, and exposure in pregnant women who have no immunity has resulted in hydrops fetalis and stillbirths. Therefore, isolation precautions must be taken for pregnant staff.

Acute Splenic Sequestration

The diagnosis of acute splenic sequestration is based on sudden enlargement of the spleen along with a greater than 2-g/dL (20-g/L) decrease in Hb from baseline with reticulocytosis. Thrombocytopenia also may be present. The rapidity of the event can result in sudden circulatory collapse and was a common cause of death prior to early diagnosis and education through newborn screening programs. Splenic sequestration occurs in children younger than 3 years of age who have Hb-SS and in the other Hb S variants at all ages, and recurrence is frequent. The emergent management of severe splenic

identified the cause in 38% of patients. Infection accounted for ACS in 29% of patients, with agents including bacteria, viruses, *Mycoplasma*, and *Chlamydia*. Fat embolism occurred in 9% of patients. VOC was the admitting diagnosis in 50% of patients who had ACS. The findings of pulmonary fat embolism suggest that bone marrow infarction with fat embolization to the lung is a cause of ACS associated with VOC. Further, the known complications of hypoventilation associated with opioid administration for SCD pain crises add to the risk of VOC-associated ACS.

The treatment for ACS includes broad-spectrum antibiotics, including a cephalosporin and macrolide, as well as oxygen, hydration, incentive spirometry, and early intervention with simple transfusion therapy for associated hypoxia or a hematocrit less than 18% (0.18). Exchange transfusion is reserved for patients who have progressive, multilobe infiltrates and hypoxia. Multiple ACS episodes may lead to chronic restrictive pulmonary disease and possibly to pulmonary hypertension. Children who have recurrent ACS should be evaluated with pulmonary function studies by a pediatric pulmonologist.

Cerebrovascular Disease

Neurologic complications are a significant cause of morbidity in children who have SCD. Overt stroke occurs in 11% of patients who have Hb-SS by age 20 years, and silent infarction is detected on

neuroimaging studies in another 22%. The peak incidence of overt stroke occurs in children between 2 and 10 years of age and involves large-artery disease of the internal carotid and anterior and middle cerebral arteries of the Circle of Willis. Overt stroke is ischemic or thrombotic in 75% of patients who have Hb-SS, predominantly children, and hemorrhagic in 25%, usually adults. Chronic transfusion therapy to maintain the Hb S concentration below 30% prevents a second stroke in 80% of pediatric patients.

Transcranial Doppler (TCD) ultrasonography can detect children at risk for overt stroke before they become symptomatic when they have flow velocities greater than 200 cm/sec. A multicenter study of TCD screening and transfusion therapy, the Stroke Prevention Trial in SCD (STOP), demonstrated that 10% of children who had Hb-SS and -S-beta⁰ thalassemia had TCD velocities greater than 200 cm/sec and that chronic transfusion therapy could decrease primary stroke 10-fold in this

sequestration with circulatory collapse should include the use of volume expanders such as normal saline bolus while awaiting compatible blood for transfusion. Today, parental education about clinical signs of splenic sequestration and physical palpation of spleen size plus the judicious use of transfusions and splenectomy in patients who have had two or more events has decreased the death rate from sequestration significantly in children who have SCD.

Acute Chest Syndrome

Acute chest syndrome (ACS) is the second leading cause of hospital admission in SCD after VOC pain crises. Approximately 50% of patients who have SCD experience at least one episode of ACS. Although ACS is more common in children, it is more severe in adults. ACS is defined by the radiologic appearance of a new pulmonary infiltrate and fever. Hypoxia may be present but is not necessary for the diagnosis. A multicenter study of ACS

The emergent management of severe splenic sequestration with circulatory collapse should include the use of volume expanders. . . .

high-risk group. TCD screening for stroke risk is recommended in all children who have Hb-SS or -S-beta⁰ thalassemia between ages 2 and 16 years, and transfusion therapy should be offered to those who have a TCD velocity greater than 200 cm/sec with or without stenosis on magnetic resonance arteriography. A follow-up study to STOP demonstrated that discontinuation of transfusion therapy after 36 months of therapy resulted in reversion to abnormal TCD velocity or stroke in 45% of patients. Current guidelines recommend indefinite transfusion therapy for patients who have abnormal TCD findings.

The other major neurologic complication in SCD is the silent infarction of white matter seen on magnetic resonance imaging (MRI) in 22% of Hb-SS patients. This infarction is the result of sickling in the microcirculation and is unlike the large-vessel disease of overt stroke. Such lesions usually are accompanied by neuropsychometric deficits that lead to learning and cognitive problems. Evidence suggests that silent infarction is associated with an increased risk of overt stroke, and the use of transfusion therapy as a preventive measure for silent infarction is being investigated in a multicenter clinical trial.

VOC Pain Crises

The VOC pain crisis is the hallmark of SCD. It is the most distressing symptom to patients and leads to debilitation and impaired functioning in school, on the job, and socially. The spectrum of VOC among SCD patients is wide, with some 34% of patients experiencing one or fewer VOCs per year and another 5% experiencing multiple events, accounting for 30% of SCD admissions to the hospital. Frequent hospital admissions for VOC (>6/y) are a known risk factor for early death in SCD. VOC episodes may be triggered by infection, temperature extremes, dehydration, or emotional stress, but often there is no identifiable cause. Multidisciplinary management of VOC should involve hematologists, pain specialists, social workers, and psychologists. Hospital management should include aggressive pain management with age-appropriate patient-controlled analgesia and the use of opioids (morphine or hydromorphone), nonsteroidal anti-inflammatory agents (ibuprofen or ketorolac), hydration, physical therapy, and ancillary therapies such as relaxation or guided imagery.

The average length of hospitalization for VOC in children is 4 days. Chronic pain syndromes may occur in a minority of patients and usually are due to recurrent VOC of bones as well as to undertreatment of acute pain. Patients experiencing more than 10 days of hospitaliza-

tion with opioid treatment may become tolerant and need to be weaned from opioids slowly. Long-acting opioids such as methadone and agents that decrease the adverse effects of withdrawal have a role in the management of chronic pain syndromes.

Chronic Organ Damage

The increased survival of patients who have SCD has emphasized focusing on the problems of chronic organ damage that may present from adolescence onward. The most serious emerging complication is pulmonary artery hypertension (PAH), which is associated with a mean pulmonary artery pressure greater than 25 mm Hg or a tricuspid jet velocity on echocardiography greater than 2.5 m/sec or both. PAH may occur in up to 30% of young adults who have Hb-SS and is associated with chronic hypoxia, dyspnea, and syncope. In the early stages, however, it is asymptomatic. In a small study, the NIH found the median survival after diagnosis to be 2 years.

PAH is a disease of the large pulmonary artery, whose histology is similar to the cerebral arteriopathy of stroke in SCD. Abnormalities in nitric oxide bioavailability due to a hyperhemolytic state are postulated as one mechanism leading to the development of PAH in patients who have hemoglobinopathies. Elevation in the biomarker pro-brain natriuretic peptide (BNP) to a concentration greater than 160 pg/mL in patients who have SCD is correlated with a 78% positive predictive value for the diagnosis of PAH and is predictive of increased mortality. BNP is a hormone released in response to stretching of the cardiac myocytes, and high concentrations reflect volume and chamber overload. Therapies directed at suppressing hemolysis, such as transfusion and hydroxyurea, are proposed. Clinical trials aimed at increasing nitric oxide-mediated vasodilatation with agents such as sildenafil citrate also are planned.

Other chronic organ damage commonly seen in SCD (Table 3) includes osteonecrosis of the femoral and humeral heads, which occurs in 50% of those who have Hb-SS by age 35 years, with an increased risk for those who have Hb-SS and alpha thalassemia. Approximately 60% of patients who have Hb-SC develop osteonecrosis by age 60 years. Proliferative retinopathy is more common in Hb-SC; approximately 50% of patients develop retinopathy. Renal abnormalities of glomerular and tubular functions leading to hyposthenuria are common in all sickle syndromes, and nephrotic syndrome and end-stage renal disease can occur in 5% to 10% of Hb-SS patients. Chronic leg ulcers occur in 10% to 25% of Hb-SS patients, priapism in 10% to 40% of adult males,

and cholelithiasis in 42% by adolescence. Although cholelithiasis is a common finding in patients who have SCD, cholecystectomy is indicated only in those suffering abdominal pain or cholestatic jaundice due to common duct obstruction. Patients who present with cholecystitis should be treated with antibiotics and supportive care and be referred for elective cholecystectomy weeks after the acute event.

Prevention

Health-care maintenance for children and adolescents who have SCD requires a multidisciplinary team of pediatric hematologists, nurse practitioners, social workers, psychologists, and genetic counselors working with primary care practitioners. Children who have SCD require the pediatric services given to all children as well as the specialized immunizations, subspecialty evaluations, and psychosocial services specific for sickle cell complications (Table 2). Infants who have SCD now are identified routinely by newborn screening programs and should be

Infants who have SCD now are identified routinely by newborn screening programs . . .

evaluated in an SCD program by 3 months of age. Specific interventions aimed at prevention of major complications of SCD, such as bacterial infection and stroke, are mandated by NIH recommendations. Penicillin prophylaxis should be instituted no later than 3 months of age and continued to age 5 years. Immunization with the 23-valent pneumococcal vaccine should be administered at ages 2 and 5 years, in addition to the heptavalent conjugated pneumococcal vaccine at 2, 4, and 6 months of age. TCD ultrasonographic evaluation for stroke risk should begin at age 2 years in patients who have Hb-SS and -S-beta⁰ thalassemia. Routine screening evaluations for chronic end-organ damage should start in mid-childhood. Parental education regarding SCD complications is imperative, especially for the young child who is at greater risk of pneumococcal sepsis and splenic sequestration.

Therapies

Transfusion

Transfusion therapy frequently is used transiently in SCD to treat acute manifestations of the disease, such as

aplastic crises, splenic sequestration, and ACS. Transfusion also can be used chronically to prevent stroke. Although lifesaving, transfusion also is associated with iron overload, alloimmunization, and potential infectious complications. If transfusion therapy is not used judiciously, it is potentially dangerous due to the hyperviscosity of the sickle hemoglobin. Therefore, guidelines for simple transfusion of packed red blood cells (PRBC) in SCD recommend that the final hematocrit after a transfusion not exceed 30% (0.30) and that all transfusions be performed under the guidance of a pediatric hematologist. Transfused blood should be sickle-negative, matched for CDE and Kell antigens, and leukoreduced.

Clinical situations in which simple PRBC transfusion is recommended include aplastic crises, splenic sequestration, ACS, and preoperatively for most surgical procedures. Chronic transfusion therapy is used to maintain Hb S below 30% in patients who have clinical stroke and positive TCD findings and possibly in patients experiencing pulmonary hypertension. Exchange transfusion is reserved for stroke presentation; severe ACS; unremitting priapism; and preoperative neurologic, cardiac, and retinal surgery.

SCD patients receiving chronic transfusion experience iron overload, usually after 1 year of monthly transfusion. Chelation therapy with deferoxamine or the new oral iron chelator deferasirox (Exjade[®]) (Novartis Pharmaceuticals, Basel, Switzerland) should be instituted at that time. The consequences of untreated iron overload include cardiomyopathy, cirrhosis, diabetes mellitus, and early death.

Hydroxyurea

The amelioration of SCD complications by elevated concentrations of fetal Hb in newborns and in individuals genetically programmed to maintain fetal Hb production initiated a search for compounds that would increase fetal Hb in vivo. Hydroxyurea (HU), an S-phase cytotoxic drug used predominantly to treat chronic myelogenous leukemia and polycythemia vera, is such an agent. The effectiveness of HU in treating SCD was demonstrated by a multicenter phase III trial in adults who had severe SCD in whom HU therapy decreased the frequency of VOC, ACS, hospital admissions, and need for blood transfusions by 50%. HU now is approved by the United States Food and Drug Administration (FDA) for adults who have SCD.

Pediatric phase II studies of HU have demonstrated improvement in the same hematologic parameters as the adult study, with increases in Hb and fetal Hb and decreases in leukocytes, platelets, and reticulocytes. A phase III study that examines the effectiveness of HU in preventing organ damage and maintaining elevated fetal Hb concentrations in children who have Hb-SS from 9 to 18 months of age at enrollment is ongoing in the United States. Another NIH-sponsored trial examining the effectiveness of HU compared with chronic transfusion therapy in secondary stroke prevention is ongoing. Early evidence suggests that HU may preserve some splenic function in children younger than 2 years of age, but also may increase the risk of splenic sequestration.

At present, HU is used in children older than 5 years who have severe complications of SCD and should be prescribed only under the guidance of a pediatric hematologist. Because HU is a cytoreductive agent, it should be administered in a structured medical environment with attention to compliance and escalation of doses to 30 mg/kg or the maximum tolerated dose. Long-term complications of HU are unknown; potential leukemogenic and growth restriction effects in young children require conservative selection of patients for HU therapy.

Hematopoietic Stem Cell Transplant

The only cure for SCD today is hematopoietic stem cell transplant (HSCT), which requires a human leukocyte antigen-matched sibling donor. The indications for HSCT include stroke, positive TCD result, and multiple ACS or VOC episodes. Ideally, HSCT should be performed early, before end-organ complications such as iron overload or chronic pulmonary disease occur. The event-free survival in SCD patients receiving HSCT is 95%. Unfortunately, only 14% of SCD patients who have indications for HSCT have an HLA-matched donor sibling. Eventually, improved survival with other HSCT modalities, such as umbilical cord blood transplantation, haploidentical transplants, and nonmyeloablative conditioning regimens, may augment sibling donor protocols and widen the availability of HSCT and potential cure to SCD patients.

Predictors of SCD Complications

The judicious choice of current treatments for SCD could be aided by the ability to predict disease severity in Hb-SS patients at a young age. Clearly defined genetic modifiers of SCD include elevated fetal Hb concentrations sustained at greater than 20% and alpha thalassemia. Fetal Hb inhibits sickle polymer formation and results in an increased hematocrit, ameliorating most

SCD complications. Alpha thalassemia results in a higher hematocrit, and while protective against stroke, is associated with osteonecrosis and splenic sequestration. Clinical predictors of severe disease were identified by the Cooperative Study of Sickle Cell Disease as dactylitis (painful swelling of the hands and feet) before 1 year of age, an elevated steady-state leukocyte count, and a steady-state Hb concentration of less than 7 g/dL (70 g/L). Patients having these indicators had multiple adverse outcomes, such as death (26%), stroke (36%), frequent VOC (24%), and recurrent ACS (14%).

Future Therapies

New treatments for SCD are directed at ameliorating the secondary events related to sickling as well as finding new fetal Hb-modulating agents. Clinical trials are in progress or planned to moderate red blood cell dehydration by blocking the Gardos channel, increase nitric oxide bioavailability, and evaluate new compounds that augment fetal hemoglobin production.

Conclusion

SCD is a hereditary chronic hemolytic anemia in which polymerizations of sickle Hb result in a misshapen, less deformable, sickle red blood cell; vascular occlusion; and ischemia of many major organ systems. The clinical heterogeneity among patients who have SCD is substantial. The life expectancy of affected individuals has tripled over the last 3 decades, due primarily to early identification through newborn screening programs and decreased death rates from pneumococcal sepsis. The increase in life expectancy has shifted focus to the chronic end-organ damage now seen in adolescents and adults. HSCT from a matched sibling donor is curative for SCD but is available only to a minority of patients. HU is the only FDA-approved treatment for adults who have SCD, and clinical trials are ongoing to examine HU therapy in young children who have SCD. New therapies designed to interfere with sickle polymerization and moderate its ancillary effects are planned or in progress.

Suggested Reading

- Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med.* 1998;339:5–11
- Ashley-Koch A, Yang Q, Olney RS. Sickle hemoglobin allele and sickle cell disease: A HuGE Review. *Am J Epidemiol.* 2000;151:839–845
- Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med.* 2004;350:886–895

- Machado RF, Anthi A, Steinberg MH, et al. N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease. *JAMA*. 2006;296:310–318
- Miller ST, Sleeper LA, Pegelow CH. Prediction of adverse outcomes in children with sickle cell anemia. *N Engl J Med*. 2000;342:83–89
- Powers DR, Chan LS, Hiti A, et al. Outcome of sickle cell anemia. *Medicine*. 2005;84:363–375
- Steinberg MH. Management of sickle cell disease. *N Engl J Med*. 1999;340:1021–1030
- Steinberg MH, Barton F, Castro O, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia. *JAMA*. 2003;289:1645–1651
- Stuart MJ, Nagel RL. Sickle cell disease. *Lancet*. 2004;364:1343–1360
- Vichinsky EP. New therapies in sickle cell disease. *Lancet*. 2002;360:629–631
- Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. *N Engl J Med*. 2000;342:1855–1865
- Wilimas JA, Flynn PM, Harris S. A randomized study of outpatient treatment with ceftriaxone for selected children with sickle cell disease. *N Engl J Med*. 1993;329:472–476

PIR Quiz

Quiz also available online at www.pedsinreview.org.

12. A 14-month-old boy who has sickle cell disease (SCD) developed a fever to 104°F (40°C) 3 hours ago. He has had nasal congestion for 2 days but no fever. He had been drinking normal amounts of fluids until he became febrile and since has taken only very small amounts. His physical examination reveals normal blood pressure. Oxygen saturation is 96% in room air. The only abnormalities are possible crackles over the right upper lobe and a spleen palpable 1 to 1.5 cm below the left costal margin. Complete blood count reveals a hemoglobin of 6.9 g/dL (69 g/L), white blood cell count of $18 \times 10^3/\text{mCL}$ ($18 \times 10^9/\text{L}$), and platelet count of $675 \times 10^3/\text{mCL}$ ($675 \times 10^9/\text{L}$). Blood culture is obtained. Of the following, the *most* appropriate initial step is to:
- Administer a bolus of normal saline over 1 hour.
 - Administer intravenous ceftriaxone.
 - Ensure that prophylactic penicillin has been administered and is continued.
 - Obtain a chest radiograph.
 - Transfuse packed red blood cells.
13. The mother of a 2-year-old boy who has SCD noted decreased activity and increasing pallor in the boy over the past 8 hours. She has been taught splenic palpation, and she reports that his spleen usually is not palpable, but was 3 inches below the rib cage before leaving home. Physical examination reveals a pale, lethargic child. His temperature is 100.4°F (38°C), heart rate is 195 beats/min, respiratory rate is 40 breaths/min, and blood pressure is 60/32 mm Hg. He is crying, and the edge of his spleen appears to be 6 cm below the left costal margin. A blood count, blood culture, and cross-match are obtained. Of the following the *most* appropriate next step is:
- A bolus of intravenous normal saline.
 - Intravenous ceftriaxone followed by vancomycin.
 - Transfusion of antigen-matched packed red blood cells.
 - Transfusion of uncrossed-matched, O-negative packed red blood cells.
 - Urgent ultrasonography to confirm splenic enlargement.
14. Parents of a newborn in whom SCD was diagnosed by newborn screening come to you for counseling and education. Although they understand that the first painful event is not likely to occur for at least several months, they are concerned about their child's future if painful events should begin early. Which of the following types of pain is a clinical predictor of severe disease if it occurs before 1 year of age?
- Abdominal tenderness.
 - Chest tenderness and increased respiratory rate.
 - Hip pain.
 - Painful swelling of the hands and feet.
 - Priapism.

15. The parents of an 8-year-old girl who has SCD meet with you because she has had at least five hospital admissions annually for vaso-occlusive pain crises or acute chest syndrome for the past 3 years. She has no siblings. Of the following, the *most* appropriate recommendation for this child is:
- A. A chronic transfusion program.
 - B. A Gardos channel blocker.
 - C. A 3-month trial of monthly red cell transfusions.
 - D. Hematopoietic stem cell transplant using a matched, unrelated donor.
 - E. Hydroxyurea.
16. Results of transcranial Doppler ultrasonography in a 4-year-old boy who has SCD reveal flow velocities of more than 200 cm/sec in several major intracerebral arteries. Results of a prior study 1 year ago were normal. The imaging is repeated, and the flow velocities remain elevated. Of the following, the *most* appropriate recommendation at this time is to:
- A. Begin a chronic red cell transfusion program.
 - B. Begin both hydroxyurea and transfusions, changing to hydroxyurea alone after 6 months.
 - C. Begin hydroxyurea.
 - D. Give a single red cell transfusion and repeat the Doppler study.
 - E. Obtain magnetic resonance imaging/angiography of the brain and, if results are normal, observe the child for 6 months.