Sickle Cell Disease

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Educational Gap

In the United States, sickle cell trait is carried by 7% to 8% of people of African ancestry, and the sickle hemoglobinopathies are estimated to affect 90,000 to 100,000 people.

Objectives

After completing this article, readers should be able to:

1. **Understand how the sickle hemoglobin mutation leads to the various manifestations of sickle cell disease (SCD).**
2. **Identify common health maintenance needs for children with SCD.**
3. **Recognize the common acute complications of SCD and their treatment.**
4. **Assess the risks and benefits of the common treatment modalities for SCD.**
5. **Discuss the improved prognosis for children with SCD.**

Abbreviations

ACS:	acute chest syndrome
Hgb:	hemoglobin
HgbS:	sickle hemoglobin
HSCT:	hematopoietic stem cell transplantation
HU:	hydroxyurea
IPD:	invasive pneumococcal disease
PAH:	pulmonary artery hypertension
PCV13:	pneumococcal conjugate vaccine
PROPS:	Prophylactic Penicillin Study
RBC:	red blood cell
SCD:	sickle cell disease
SS:	sickle cell anemia
Sβ^0:	sickle β^0 thalassemia
TCD:	transcranial Doppler
TRJV:	tricuspid regurgitant jet velocity
VOC:	vaso-occlusive crises

Epidemiology

The World Health Organization estimates that 7% of the world's population carries a hemoglobin (Hgb) mutation and that 300,000 to 500,000 children are born each year with severe hemoglobinopathy. The sickle Hgb (HgbS) mutation occurred independently at least four times (three times in sub-Saharan Africa and once in India or the Arabian peninsula) in regions with endemic malaria. In the heterozygous state, the sickle mutation provides protection against infection by the *falciparum* species of malaria and likely confers a survival advantage, leading to its continued high prevalence in some populations of sub-Saharan Africa and the Middle East/India. In the United States, sickle cell trait is carried by 7% to 8% of people of African ancestry, and the sickle hemoglobinopathies are estimated to affect 90,000 to 100,000 people. (1) US newborn screening data suggest that 1 in 2,500 newborns is affected by a form of sickle cell disease (SCD).

Nomenclature

SCD refers to a group of heterogeneous disorders that are unified by the presence of at least one β globin gene affected by the sickle mutation (position 6, β-globin gene; codon GAG changes to codon GTG, coding for glutamic acid instead of valine). Homozygotes for the sickle mutation have sickle cell anemia (SS) or Hgb SS disease, which accounts for ~60% to 65% of SCD.

When inherited with the sickle mutation in a compound heterozygous state, other β-globin gene mutations lead to other distinct forms of SCD. The most common of these is HgbC, which, when coinherited with the sickle mutation, leads to sickle hemoglobin-C disease, accounting for 25% to 30% of all SCD. Coinheritance of a β thalassemia mutation with the sickle mutation leads to sickle β^0 thalassemia (Sβ^0) or sickle β^+ thalassemia, which account for 5% to 10% of all SCD (β^0 indicates no β globin production; β^+ indicates diminished β globin production).

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Other less common β-globin mutations that lead to SCD when coinherited with HgbS include Hgbs O^{Arab}, D, and E. When discussing patients with SCD, precise nomenclature is important because of the phenotypic variability between the various forms.

It should also be noted that the term "sickler" is viewed as a derogatory term by many in the SCD clinician and patient community and is inappropriate to use in communication among clinicians. More appropriate terminology would be "a patient with sickle cell disease."

Pathophysiology

The sickle mutation leads to the replacement of hydrophilic glutamic acid by a hydrophobic valine. The presence of the hydrophobic valine residue allows HgbS to polymerize in the deoxygenated state. In addition to low oxygen tension, low pH and an increased concentration of HgbS within the red blood cell (RBC) encourage polymer formation. HgbS polymerization ultimately causes RBCs to take on the characteristic sickle shape in a reversible fashion. Repeated episodes of polymerization and "sickling" can cause an RBC to be irreversibly sickled. In the circulation, these stiff, nondeformable sickled cells can lead to vaso-occlusion, with resultant tissue ischemia. As a result of or in addition to HgbS polymerization, other pathophysiologic mechanisms in patients with SCD have been observed, including activation of the vascular endothelium, leukocytosis, leukocyte activation, platelet activation, and oxidative stress from tissue reperfusion. Additionally, reduced RBC deformability and injury of the RBC cytoskeleton caused by the presence of HgbS polymers ultimately result in both intravascular and extravascular hemolysis. In the past 10 years, it has been suggested that nitric oxide depletion secondary to intravascular hemolysis may contribute to certain complications of SCD, such as pulmonary artery hypertension (PAH), although this postulate is controversial. (2)(3)

Diagnosis

Before newborn screening, the diagnosis of SCD was made only after a potentially devastating complication prompted medical attention. Justification of newborn screening for SCD was provided by the Prophylactic Penicillin Study (PROPS) in 1986 (see below), and since then, universal newborn screening with Hgb electrophoresis (Table 1) or other methods has become the standard in the United States. Certain states also provide confirmation of an SCD electrophoresis result by DNA sequencing. As with most genetic conditions, prenatal diagnosis of a fetus with SCD is possible in the first trimester through chorionic villus sampling or in the second trimester through amniocentesis.

Table 1. Newborn Screen Results for Common Hemoglobinopathies

Newborn Screening Result	Interpretation
F, A	Normal
F, A, S	Sickle cell trait
F, S	SS, $S\beta^0$, or S-HPFH
F, S, C	HgbS-C disease
F, S, A	Sickle β^+ thalassemia
F, A, S, Barts	Sickle cell trait with α thalassemia trait
F	β-thalassemia major

β thalassemia trait is not diagnosed in the newborn period with most current newborn screening techniques. A=HgbA; C=HgbC; F=fetal Hgb; S=HgbS; S-HPFH=sickle with hereditary persistence of fetal Hgb.

Health Maintenance

SCD is medically complex, affecting virtually any organ in the body, so children born with SCD benefit from well-coordinated, comprehensive, multidisciplinary care. This care occurs ideally through regular interactions with both a primary care provider and a pediatric hematologist. Psychologists, social workers, and expert nursing support play important roles as patients and families adjust to life with SCD and its complications. Additionally, other subspecialty expertise in SCD is important, including neurology, pulmonology, nephrology, radiology, ophthalmology, otorhinolaryngology, general surgery, and anesthesiology. In addition to the elements of routine health maintenance highlighted in Table 2, common chronic problems and activities discussed at routine visits include enuresis, sleep and sleep-disordered breathing, jaundice, mental health and adjustment to chronic disease, and sports participation. In the teenage years, fostering self-care, responsibility, and readiness for transition to adult care become the focus.

Clinical Presentation

Effects on Blood

A variety of hematologic abnormalities typify SCD. Anemia is the primary hematologic manifestation of SCD, with the severity determined by genotype (Table 3), in addition to the specific patient's rates of hemolysis, erythropoiesis, and plasma volume expansion. (4) After the transition to adult β globin expression occurs in the first

Table 2. Health Maintenance Timeline for Children With SCD

Intervention/Activity	Timing
Comprehensive medical evaluation (with a hematologist, where possible)	First visit by 2 mo of age 3–4 / y until age 5 1–2 / y after age 5
Genetic counseling	First visit, re-educate as needed
Pneumococcal prophylaxis	
Twice daily prophylactic penicillin	As soon as possible
PCV13 series	2, 4, 6, and 12–15 mo
Pneumococcal polysaccharide vaccine	First dose at 2 y of age
Haemophilus influenzae type b vaccine	2, 4, 6, and 12–15 mo
Meningococcal vaccine (MCV4)	1st dose at 24 months of age or older; 2 total doses at least 8 weeks apart
Influenza virus vaccine	First after 6 mo after birth, annually thereafter
Education on spleen palpation and signs/symptoms of splenic sequestration	First visit and every visit thereafter until age 3–5 y
TCD ultrasonography*	First screen at 2 y of age If normal, repeat annually until age 16 If conditional, repeat every 3–6 mo If abnormal ×2, initiate transfusions
Asthma screening	Screening history at 1 y of age, then annually PFTs at 6 y of age, then every 5 y†
Growth and maturation assessment	At least annually
Assessment of school performance	At least annually upon school entry
Assessment for sickle retinopathy by an ophthalmologist	Annually beginning at 10 y of age
Evaluate for sickle nephropathy by creatinine, urinalysis, urine protein/creatinine ratio or microalbuminuria‡	Annually beginning at 10 y of age‡
Counseling on transition to adult care‡	Annually beginning at 13–15 y of age‡
Screening performed at some centers	If done, ideal timing is unknown
History, physical or radiograph for avascular necrosis of femoral heads	
History and physical for obstructive sleep apnea	
Echocardiography for elevated TRJV	
MRI for silent stroke and cerebral vasculopathy	

PFT=pulmonary function test, TCD=transcranial Doppler.
*For patients with SS and $S\beta^0$.
†Disagreement among experts about the necessity of PFT screening.
‡Limited evidence base to support a specific method or timing.

year of life, children with SCD typically maintain stable baseline Hgb levels with significant fluctuations occurring usually during acute disease complications. Additionally, a leukocytosis with typical total white blood cell counts of 15,000 to 25,000/mm^3 is observed. A mild thrombocytosis is also common among patients with SCD, with average platelet counts of 400,000 to 475,000/mm^3.

Infection

PNEUMOCOCCUS AND PROPHYLACTIC PENICILLIN. A predilection to infection by the encapsulated organism *Streptococcus pneumoniae* has long been recognized in children with SCD, particularly those with SS, due to functional asplenia. Before attempts at prophylaxis, the incidence of invasive pneumococcal disease (IPD) was six episodes/100 patient years, with a peak in the first 3 years of life. Beginning in the late 1970s and early 1980s, the pneumococcal polysaccharide vaccine became standard for children with SCD. In 1986, the landmark PROPS clinical trial revealed an 84% decrease in the risk of IPD in children receiving daily prophylactic penicillin, compared with those receiving placebo. (5)

The PROPS II study attempted to answer the question of whether prophylactic penicillin could be discontinued safely at 5 years of age. (6) The number of IPD events was unexpectedly low during the study period, so a difference in the rates of IPD between groups could not be demonstrated clearly. This finding has led to a variable practice among sickle cell centers with some

Table 3. **Hematologic Parameters for the Common Forms of SCD**

Name	Genotype	Typical Baseline Values		
		Hgb, g/dL	Reticulocytes, %	MCV
Sickle cell anemia	SS	6–9	10–20	Normal*
Sickle hemoglobin-C disease	SC	9–11	3–10	Low normal to slightly low
Sickle β-zero thalassemia	$S\beta^0$	6–9	10–20	Low
Sickle β-plus thalassemia	$S\beta^+$	10–12	2–5	Low

MCV=mean corpuscular volume.
*Unless α thalassemia trait is coinherited with SS.

recommending daily penicillin for life (or at least until age 18 years), whereas others recommend cessation of prophylaxis at age 5 years. Similarly, the role of penicillin in patients with Hgb SC and other mild genotypes is controversial.

The heptavalent pneumococcal conjugate vaccine, licensed in 2000, has led to a further 70% decrease in the incidence of IPD, now estimated to be 0.3 to 0.5/100 patient years. (7) After heptavalent pneumococcal conjugate vaccine licensure, nonvaccine serotypes emerged as the most common cause of IPD, particularly serotype 19A. Pneumococcal conjugate vaccine (PCV13), licensed in 2010, includes 19A and other currently prevailing serotypes. Current standard practice should include daily prophylactic penicillin beginning before 2 months of age, the PCV13 series as recommended for all children, and at least two doses of pneumococcal polysaccharide vaccine, with the first dose at 2 years of age.

FEVER MANAGEMENT. Because of the risk of IPD, any fever (typically defined as ≥38.3°C) is treated as a medical emergency for children with SCD. Urgent evaluation of all febrile episodes, including physical examination, complete blood count, and blood culture, is of utmost importance. Although hospitalization for observation is sometimes necessary, patients with SCD evaluated for fever without a source who lack certain high risk features (white blood cell count >30,000/mm³ or <5,000/mm³, fever >40°C, "ill-appearing") may be managed safely as an outpatient after intravenous administration of an empiric, antipneumococcal antibiotic (eg, ceftriaxone). Other factors that must be considered in deciding whether to discharge a patient from the emergency department include the age of the patient, the ability of the family to return promptly for recurrent fever or clinical deterioration, and the availability of close follow-up.

APLASTIC CRISIS. Infection by parvovirus B19 leads to a maturation arrest for RBC precursors in the bone marrow for ~10 to 14 days. In hematologically normal children, this arrest in RBC production is not problematic because of the 120-day lifespan of normal RBCs. In SCD, however, the RBC lifespan is between 10 and 20 days, so cessation of RBC production for 10 to 14 days can lead to profound anemia. Signs and symptoms of profound anemia, including pallor, fatigue, decreased activity, altered mentation, and poor feeding, are typical of aplastic crises. Laboratory evaluation reveals severe anemia with reticulocytopenia and occasional thrombocytopenia. The management of an aplastic crisis includes transfusion support as needed until reticulocyte recovery has occurred. Family members of patients with SCD who are experiencing an aplastic crisis should be evaluated if they have SCD and no previous history of parvovirus infection.

Acute Pain

VASO-OCCLUSIVE CRISIS. Severe, episodic pain is the clinical hallmark of SCD. Commonly referred to as vaso-occlusive crises (VOC), these episodes can occur from infancy until old age, although they increase in frequency throughout childhood with a peak in the mid 20s. The pathophysiologic mechanism for most VOC is bone marrow ischemia with resultant infarction. Risk factors for more frequent VOC include severe genotype (SS or $S\beta^0$), increasing age, and high baseline Hgb level. On the other hand, a high baseline fetal Hgb concentration is protective. VOCs are triggered commonly by infection, emotional stress, or exposure to cold, wind, or high altitude. The episodes may occur in many locations throughout the body, although the lower back, legs, and arms are most common. Using the frequency of interactions with the health-care system as a proxy for pain frequency and severity may vastly underestimate the problem of pain in SCD. It is, therefore, crucial that health-care providers specifically assess pain occurring at home during routine visits.

The severity and duration of VOCs vary from minor pain lasting minutes to excruciating pain lasting days. Examination of a patient having a VOC may reveal erythema, edema, joint effusions, or point tenderness, but none of these signs may be present and they are not required for the diagnosis. A minor decrease in Hgb concentration from baseline and an increased white blood cell count are common but nonspecific laboratory features.

The approach to treating severe acute pain, sadly, has not changed in decades. Opioid analgesics, anti-inflammatory medications, and intravenous fluids remain the mainstays of treatment. RBC transfusions, however, do not aid in the resolution of severe VOCs. Recognition and treatment of psychosocial contributors to acute and chronic pain are other key elements to VOC management. Many pain crises can be treated at home with distraction and other coping behaviors in addition to oral pain medications. Prevention of VOCs can be aided by the avoidance of precipitating factors, the use of hydroxyurea (HU, see below), and maintenance of intravascular volume through oral fluid intake.

DACTYLITIS. Dactylitis is a specific type of VOC that occurs in infants and young children with SCD, especially SS. Dactylitis is defined by tender, erythematous, and edematous hands or feet (Fig 1). It occurs in 25% of infants by 1 year of age and 40% by 2 years of age, although significant variability in the prevalence has been noted among studies. Principles of dactylitis management do not differ from other VOCs; analgesics and intravenous fluids are key. Dactylitis before 1 year of age was identified as one of three prognostic factors used to predict severe outcome (frequent VOCs, frequent acute chest syndrome [ACS], acute stroke, or death) in a large cohort study of pediatric patients with SCD in the United States, although this finding could not be replicated in a large independent pediatric cohort study.

Pulmonary Complications

ACUTE CHEST SYNDROME. The very term ACS suggests an incomplete understanding of this phenomenon. Clinically, ACS is defined by a new pulmonary infiltrate (Fig 2) on chest radiograph in addition to one or more of the following: fever, tachypnea, dyspnea, hypoxia, and chest pain. ACS is a common and potentially lethal complication of SCD. The incidence of ACS is highest (25 episodes/100 patient years) in children between 2 and 5 years of age. When the underlying cause of ACS was investigated in detail including bronchoscopy, 45% of patients had no identifiable cause, whereas infection caused 30% of cases. The most common infectious causes of ACS included *Chlamydia pneumoniae* (28% of infections), viral infection (22%), and *Mycoplasma pneumoniae* (20%). Pulmonary infarction and fat embolism caused 16% and 8% of all ACS cases, respectively. The pathogenesis of ACS likely varies, depending on the cause, but commonly includes inflammation, pulmonary vascular occlusion, ventilation/perfusion mismatch, airway hyperreactivity, and pulmonary edema.

The treatment of ACS includes supplemental oxygen, empiric antibiotics (including a macrolide for coverage of atypical pathogens), bronchodilators, and careful management of analgesia and intravascular volume. Blood transfusion is another fundamental treatment for ACS. A decrease in Hgb level from baseline and an increasing

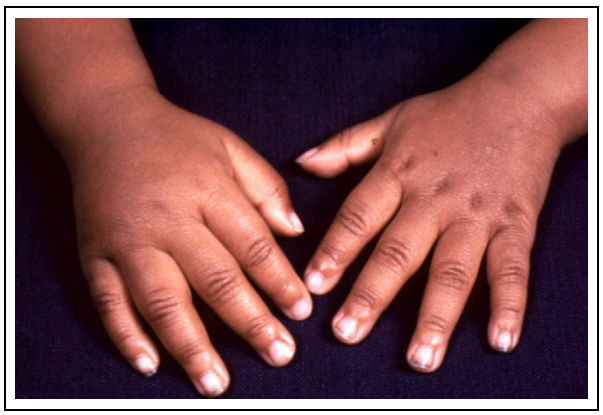

Figure 1. Dactylitis is characterized by tender, erythematous, and edematous hands or feet. Courtesy of Doernbecher Children's Hospital, Portland, Oregon.

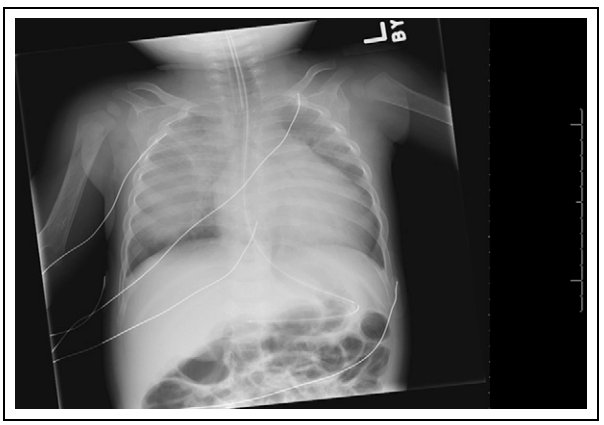

Figure 2. Chest radiograph of an 18-month-old infant with SS and severe ACS with diffuse bilateral infiltrates.

supplemental oxygen requirement are common indications for transfusion in ACS. Simple transfusion may be adequate for mild to moderate ACS, but exchange transfusion should be considered early in the course of progressive or severe ACS.

In addition to transfusion, supportive respiratory care, up to and including mechanical ventilation and extracorporeal membrane oxygenation, may be necessary in severe cases. Finally, corticosteroids have been shown to reduce the severity of ACS hospitalizations. Unfortunately, corticosteroid use is complicated by a high rate of "rebound" VOC, so if used at all, corticosteroids should be reserved for the most severe cases.

ASTHMA. Asthma is prevalent in children with SCD, as in the general population, affecting nearly 20% of patients. In SCD, a diagnosis of asthma is associated with higher rates of ACS, VOC, and early death. The mechanism by which asthma influences the severity of SCD is unclear but could relate to inflammation, ventilation-perfusion mismatching, or other mechanisms. Because of the strength of the SCD/asthma association, patients with SCD should be screened for asthma on an annual basis by history and physical examination beginning at 1 year of age. Additionally, some groups recommend screening with pulmonary function testing at least every 5 years, beginning at 6 years of age. Patients with SCD with persistent asthma also should be followed by a pulmonologist, regardless of severity.

PULMONARY ARTERY HYPERTENSION. PAH is a severe complication of SCD that typically occurs in adulthood. Its pathogenesis may relate to nitric oxide depletion secondary to release of free Hgb into the plasma from chronic intravascular hemolysis. Symptoms of PAH may include exertional dyspnea, fatigue, and syncopal events. Right heart catheterization classically has been required for the diagnosis of PAH, although an elevated tricuspid regurgitant jet velocity (TRJV) on echocardiography is correlated with catheter-determined pulmonary artery pressures. Thus, echocardiography for TRJV is used commonly as a screening test for PAH in adults with SCD, and, although controversial, has been suggested as a screening test for children with SCD as well. Abnormal TRJVs have become synonymous with PAH in some segments of the literature, but right heart catheterization is still recommended for a definitive diagnosis and before treatment of PAH.

Neurologic Manifestations

STROKE. Children with SS and Sβ^0 have long been recognized as being at risk for acute stroke. The risk of stroke is 10% in the first 20 years of life, with a peak incidence between 4 and 8 years of age. (8) Most strokes in SCD are ischemic in nature, with hemorrhagic stroke accounting for less than 10% of the total. The presenting symptoms of acute stroke in SCD include hemiparesis, facial droop, aphasia, and more generalized symptoms, including stupor and, rarely, seizure. Acute stroke symptoms may mimic a VOC in a young child reluctant to use a painful limb. The pathogenesis of acute stroke is incompletely understood but includes a vasculopathy marked by hypertrophy of the intima and media layers of the large arteries in the anterior cerebral circulation (primarily the middle cerebral arteries).

The evaluation of a patient suspected of experiencing acute stroke should include a careful history and neurologic examination; emergent radiographic evaluation by MRI or computed tomography followed by MRI when MRI is not immediately available; and a laboratory evaluation, including blood count, reticulocyte count, Hgb S percentage, and blood group and screen.

The principle underlying the treatment of acute stroke is the rapid reduction of the Hgb S percentage. This goal may be achieved through simple RBC transfusion or partial manual exchange, although automated exchange transfusion with erythrocytopheresis reduces the Hgb S percentage more efficiently and is widely regarded as standard practice. This treatment frequently leads to resolution or a marked dimunition in neurologic symptoms within 24 to 48 hours.

The long-term outcome of acute stroke is variable; many patients lack significant motor impairment but may demonstrate impaired executive functioning. A second stroke is very likely without the use of regular RBC transfusions to suppress the Hgb S percentage, and even with a chronic transfusion regimen (see below), ~20% of acute stroke victims will experience a second acute stroke. For this reason, hematopoietic stem cell transplantation (HSCT) may be an optimal therapy for children who have a history of acute stroke when a suitable donor is available (see below).

PRIMARY STROKE PREVENTION. The terrible burden of acute stroke in patients with SS and Sβ^0 has driven research dedicated to primary stroke prevention. In the early 1990s, transcranial Doppler (TCD) ultrasonography was shown to predict risk of acute stroke in SS and Sβ^0, with an abnormal TCD examination representing a 40% risk of stroke in the subsequent 3 years. In the landmark Stroke Prevention Trial in Sickle Cell Anemia, children identified to be at high risk by TCD were randomly assigned to monthly blood transfusions versus

observation, with a 90% decrease in the rate of stroke observed in the transfusion group. (9) Hence, annual screening with TCD has become standard care for children with SS and Sβ^0. The duration of transfusion is indefinite, although current studies are addressing whether patients may be transitioned safely to HU to prevent stroke.

SILENT STROKE. In the past decade, silent stroke has been recognized as an important problem in children with SS and Sβ^0. Silent stroke is defined by the presence of findings on MRI suggestive of old cerebral infarction, typically small areas of gliosis, without a corroborating clinical history of acute stroke symptoms. Silent strokes are associated strongly with neurocognitive deficits and are a risk factor for subsequent acute stroke. Most studies have revealed that silent strokes occur in ~30% of children (10) with SS and Sβ^0, leading to estimates of the cumulative prevalence of central nervous system infarct events (acute and silent stroke) of ~40% in this population. Regular blood transfusions are under study to determine whether they may decrease the risk of acute stroke in patients who have experienced silent stroke.

COGNITIVE IMPAIRMENT. Not surprisingly, patients with SCD with a history of acute stroke or silent stroke have high rates of neuropsychological dysfunction. Even the SCD population that has not been affected by acute or silent stroke has a high rate of a neuropsychological dysfunction that worsens with age, including deficits in general intelligence, attention and executive functioning, memory, language, and visual-motor performance compared with matched controls. The result may be difficulty at school and in other tasks requiring executive functioning. Early evaluation and intervention in school settings may improve outcomes for this at-risk population.

Other Clinical Sequelae

Splenic Sequestration

Rapid enlargement of the spleen with resultant trapping of the blood elements is known as acute splenic sequestration and occurs in ~30% of children with SS by 5 years of age, with most first episodes occurring before 2 years of age. Children with SC disease tend to develop splenic sequestration at 10 years of age or older. Splenic sequestration was a common cause of mortality among children with SCD before the 1980s. Education of family members in daily spleen palpation is now standard care and has increased the detection of sequestration and markedly decreased mortality.

Evaluation of a child with splenic sequestration will reveal splenomegaly, a Hgb value below baseline, and thrombocytopenia, because all blood elements will be trapped in the enlarged spleen. The management of an initial splenic sequestration episode typically includes cautious transfusion to Hgb values between 7 and 9 gr/dL. A reduction in spleen size frequently occurs 1 to 3 days after initial presentation and may lead to 2 to 3 gr/dL increases in Hgb, a phenomenon known as "auto-transfusion."

Approximately one-half of patients will experience recurrence of splenic sequestration. Splenectomy is performed commonly after a second or third sequestration episode, although some centers chronically transfuse affected infants until 2 years of age before undertaking splenectomy.

Cholelithiasis

SCD is a chronic hemolytic anemia, and when Hgb is released from the RBC, bilirubin is produced, leading to jaundice. Ultimately, this increased bilirubin is stored in the gall bladder and can precipitate to form stones. Presenting signs and symptoms of cholelithiasis in SCD include right upper quadrant or epigastric abdominal pain, jaundice, and vomiting. Incidentally discovered, asymptomatic gallstones may be observed without requiring intervention. Symptomatic stones or stones obstructing the common bile duct commonly require cholecystectomy. A laparoscopic approach is now standard for cholecystectomy, which reduces the duration of postoperative pain and hospitalization. See below for additional notes on the surgical management of patients with SCD.

Priapism

Priapism is a prolonged, painful erection of the penis with typical onset in the early morning hours. It can occur in two forms: prolonged, an episode of ≥4 hours duration, and stuttering, self-limited episodes that can occur in clusters. In SCD, priapism is thought to be caused by sickling of RBCs in the corpora cavernosa of the penis, leading to sludging and an increase in intrapenile pressure. (11) This effect, in turn, leads to local acidosis and worsening deoxygenation, which leads to further sickling in a vicious cycle that causes further outflow tract obstruction and severe pain.

Priapism can occur as young as 3 years of age, and ~30% of boys will have an episode by age 15. If a prolonged episode is left untreated, fibrosis of the cavernosa may develop, leading to permanent erectile dysfunction. Treatment of an acute episode of priapism may include

aggressive analgesia and pharmacologic efforts to decrease the vascular engorgement of the cavernosa through agents such as pseudoephredrine and etilefrine. Aspiration and irrigation of the cavernosa by a urologist may be necessary for prolonged episodes. Blood transfusions and oxygen are of unproven benefit for acute episodes of priapism.

Prevention of priapism is understudied, although nightly pseudoephedrine or etilefrine have been reported to achieve some success in case series or uncontrolled trials. Gonadotropin releasing hormone analogs also have been used to prevent recurrent priapism. The effects of HU and chronic blood transfusion for prevention of priapism are largely unreported.

Surgery

Major surgery places a child with SCD at risk of complications, including ACS. To that end, perioperative transfusion to increase the Hgb concentration and decrease the Hgb S percentage is considered standard care for major surgeries. Additionally, measures such as incentive spirometry, carefully titrated analgesia, oxygen therapy, and close inpatient observation may help decrease the risk of postoperative SCD-related complications. The role of preoperative transfusion for minor surgery including tonsillectomy/adenoidectomy is controversial, but transfusion may be safely avoided for some patients undergoing such procedures.

Therapeutics

Hydroxyurea

HU is the only medication approved by the Food and Drug Administration for the treatment of SCD. HU use for children with SCD has been reviewed recently. (12) HU was developed originally as a chemotherapeutic agent for certain leukemias and myeloproliferative diseases, but in the early 1980s, HU was recognized to increase expression of fetal Hgb. Fetal Hgb was known to inhibit the polymerization of HgbS, the primary mechanism underlying the SCD pathogenesis. HU also may act through a relative myelosuppression with a decrease in circulating neutrophils, cells whose role in the pathogenesis of some SCD complications has recently been recognized.

In clinical trials for adults with SCD, HU was shown to markedly reduce the rate of VOCs, ACS, blood transfusions, and all-cause hospitalizations. In addition, long-term follow-up studies have revealed HU to confer a survival advantage for adults with SS and $S\beta^0$. In children with SCD, the published experience with HU is less extensive, although clinical trials with HU have been conducted in children as young as 9 to 18 months of age.

A randomized clinical trial of HU for infants with SCD (BABY-HUG) was completed recently. (13) Although HU failed to improve the primary outcomes of kidney and spleen function, a decrease was observed in the rates of hospitalization, blood transfusion, ACS, dactylitis, and other VOCs for infants on HU compared with those on placebo. There is also some evidence that HU may reduce conditional and even abnormal TCD velocities.

The toxicity profile for HU has shown it to be tolerable with minimal toxicities other than the risk of mild myelosuppression. Thus, regular monitoring of blood counts is required while on HU. HU is theorized to be a teratogen as well and is contraindicated in pregnant women. Some concerns have existed in both the patient and clinician community that HU, as a chemotherapeutic agent, may induce genetic changes that could lead to myelodysplasia, leukemia, or other malignancy, yet these complications have never been attributed to HU in an actual patient with SCD. Importantly, recent analyses of peripheral blood mononuclear cells have not demonstrated impaired DNA repair mechanisms or increased mutations in children on HU compared with other patients with SCD.

In summary, HU is an important therapeutic option for children with SCD. Historically, HU was reserved only for children with severe or frequent complications of SCD, but as suggested by the authors of the recently published BABY-HUG study, consideration must now be given to offering HU to all children with SS or $S\beta^0$. (13)

Chronic Transfusion

The suppression of endogenous RBC production by regular transfusion of donor RBCs is another means by which complications of SCD may be ameliorated. The clearest indications for chronic transfusions are for both primary and secondary stroke prevention. Short- and long-term chronic transfusions also have been used to treat complications such as frequent pain, severe or frequent ACS, and growth failure, among others. Simple transfusion is the most commonly used method for RBC delivery in chronic transfusions. This method carries with it the ubiquitous problem of iron overload, because each milliliter of transfused blood contains between 0.5 and 1 mg of elemental iron, which approximates normal daily absorption. Iron loading occurs primarily in the liver, heart, and endocrine glands in patients with

SCD, and severe overload can result in morbidity and mortality.

The treatment of iron overload requires an exogenous iron chelator because humans lack a mechanism to increase excretion of the excess iron. Before 2007, the only available iron chelator (deferroxamine) in the United States required subcutaneous administration for 10 to 12 hours per day, 5 to 7 days per week. Adherence to such a medication regimen was understandably low, so severe iron overload developed in many chronically transfused patients with SCD. In 2007, an oral iron chelator (deferasirox) was licensed. Deferasirox appears to be as efficacious as deferroxamine in reducing iron burden.

In addition to iron overload, transfusion-related infection and alloantibody formation are other potential complications of chronic transfusions. Improved donor selection policies and careful nucleic acid based-testing have greatly reduced, but not eliminated, the likelihood of transfusion-related infection. The risk of alloantibody formation may be mitigated by extended RBC cross-matching and programs to match donors and recipients by race and ethnicity. Exchange transfusion, either by manual exchange or erythrocytopheresis, is an alternative to simple transfusion and appears to greatly decrease iron loading in patients on chronic transfusions.

Hematopoietic Bone Marrow Transplantation

HSCT remains the only curative option for children with SCD. Transplantation works by replacing sickle erythrocyte progenitors with normal erythrocyte progenitors in the bone marrow. HSCT typically is reserved for patients affected by severe or life-threatening complications of SCD, including stroke and ACS.

The most important risks of HSCT include peri-transplant mortality (frequently from infection), graft-versus-host disease, graft failure, and conditioning-induced infertility. Limitations to the use of HSCT include a paucity of matched siblings and poor representation of minorities in the bone marrow donor pool. Unrelated HSCT and reduced intensity conditioning regimens have been published recently but require further exploration in the clinical trial setting.

Emerging Therapeutics

Recently, a variety of new therapies have been suggested for SCD. Most tantalizing is the potential of gene therapy via the insertion of a normal β globin or γ globin gene into a patient's own hematopoietic precursors. Bone marrow has been the traditional source of hematopoietic stem cells, although the recent recognition that pluripotent stem cells may be induced from skin cells may make the production of corrected hematopoietic precursors less invasive and painful. Other emerging therapeutics currently under development for patients with SCD include novel agents aimed at inducing HgF expression, novel anti-inflammatory or antithrombotic agents to treat or prevent sickle cell complications, inhaled nitric oxide, HSCT from unrelated donors, and reduced intensity conditioning for HSCT, among others.

Quality of Care

The provision of care to patients with SCD in the United States occurs within a complex tapestry of societal and personal interactions. The acute complications of SCD lead to frequent emergency department visits and hospitalizations for some patients. Unfortunately, studies of patient experiences and clinician attitudes in both the emergency department and inpatient settings have demonstrated frequent distrust between patients and providers. Patients describe both over- and undertreatment and lack of involvement in decision-making.

The quality-of-care provided varies depending on the rarity and severity of a given complication and the experience of the hospital and its personnel with SCD patients. Recently, the first set of rigorously developed quality-of-care indicators for children with SCD were published. (14) These indicators establish a benchmark that will allow providers and health-care organizations to measure their performance in SCD care, and as changes are made to improve performance, the SCD patient's experience of care also may begin to improve.

Prognosis and Survival

In spite of the many complications that may afflict children who have SCD, their prognosis has improved in past decades. Before routine newborn screening and pneumococcal prophylaxis, death from IPD, splenic sequestration, ACS or other severe complications of SCD was a common occurrence in childhood. Recent studies from cohorts in the United States and the United Kingdom suggest that death in childhood is becoming an infrequent event, with ~95% of children with SCD surviving to age 18 years. (15) Unfortunately, the young adult years, following transition to adult care, appear to be a high-risk period for individuals with SCD, which has led to a recent emphasis on improving the transition process, with the long-term goals of improving quality of life, quality of medical care, and survival for patients with SCD.

Summary

- Sickle cell disease (SCD) is a heterogeneous group of prevalent, potentially life-threatening, chronic disorders of hemoglobin (Hgb).
- Hgb polymerization underlies the pathophysiology of SCD.
- Children who have SCD benefit from regular health maintenance visits with a pediatric hematologist and a primary care pediatrician.
- The high incidence of invasive pneumococcal disease (IPD) in SCD justifies newborn screening, daily prophylactic penicillin, and immunization with the pneumococcal conjugate and polysaccharide vaccines.
- Vaso-occlusive pain crises are the clinical hallmark of SCD and occur with increasing frequency through childhood. These episodes warrant aggressive treatment with analgesics and hydration and may be prevented with hydroxyurea (HU) therapy.
- Annual transcranial Doppler (TCD) screening for patients ages 2 to 16 years identifies those at high risk for acute stroke, and regular blood transfusions can reduce this risk greatly.
- Common indications for initiating HU therapy have been severe or frequent vaso-occlusive crises or acute chest syndrome, but this therapy may be considered in younger and less symptomatic patients.
- The prognosis for children with SCD has improved, with the vast majority surviving into adulthood, prompting a focus on improving the process of transition to adult care.

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PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Since January 2012, learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit™*. In order to successfully complete 2012 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

Starting with 2012 *Pediatrics in Review*, *AMA PRA Category 1 Credit™* can be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. Neonatal screening has identified an infant with sickle cell anemia. Which of the following is the most appropriate method of protection against invasive pneumococcal disease?
   - A. Begin daily prophylactic penicillin at 2 years of age; administer pneumococcal polysaccharide vaccine instead of pneumococcal conjugate vaccine at recommended intervals for all children.
   - B. Begin daily prophylactic penicillin at 2 years of age; pneumococcal conjugate vaccine as recommended for all children, and at least two doses of pneumococcal polysaccharide vaccine at 2 and 5 years.
   - C. Begin daily prophylactic penicillin before 2 months of age; administer pneumococcal conjugate vaccine as recommended for all children and at least two doses of pneumococcal polysaccharide vaccine at 2 and 5 years.
   - D. Begin daily prophylactic penicillin before 2 months of age; administer pneumococcal conjugate vaccine instead of pneumococcal polysaccharide vaccine at recommended intervals for all children.
   - E. Begin daily prophylactic penicillin before 2 months of age; administer pneumococcal polysaccharide vaccine at 2, 4, and 6 months of age and at least two doses of pneumococcal conjugate vaccine at 2 and 5 years.

2. A 3-year-old girl with sickle cell anemia presents with fatigue and malaise for the last 3 days. Her mother feels that the girl appears much paler than usual. Examination reveals a pale child with temperature 37.4˚C, heart rate 125 beats per minute, respirations 28 per minute, and blood pressure 90/50 mm Hg. The rest of the physical examination is unremarkable. Complete blood count reveals a hemoglobin level of 4 G/dL, WBC 5,400/μL with 34% neutrophils, 48% lymphocytes, and 18% monocytes, and platelets 250,000/μL. Reticulocyte count is 0.4%. Which of the following best explains this child's anemia?
   - A. Excessive lysis of irreversible sickle cells.
   - B. Impaired release of erythrocytes from bone marrow.
   - C. Maturation arrest of erythrocyte precursors in the bone marrow.
   - D. Replacement of bone marrow with monocytes.
   - E. Sequestration of erythrocytes in spleen.

3. A 4-year-old girl with sickle cell disease (genotype $S\beta^0$) presents with excruciating pain in both lower extremities for the last 12 hours. She describes her pain as 9/10 below the right knee and 6/10 below the left knee. She has a pet turtle, and her immunization record is unavailable. Physical examination reveals temperature 38.6˚C, respirations 26 per minute, heart rate 110 beats per minute, and blood pressure 110/78 mm Hg. There is mild erythema and moderate swelling over the upper medial surface over right tibia with point tenderness. Which of the following is the most important risk factor for this presentation?
   - A. Elevated fetal hemoglobin concentration.
   - B. Genotype $S\beta^0$.
   - C. Having a turtle as a pet.
   - D. Inadequate immunization.
   - E. Low baseline hemoglobin.

4. A 7-year-old boy with sickle cell disease (genotype SS) presents with dysphasia and right-sided weakness. Physical examination reveals normal vital signs. There is depression of right angle of mouth and weakness of right upper and lower extremities. Which of the following annual screening tests would have been most helpful in predicting the risk of this complication?

   A. Comprehensive examination by neurologist.
   B. Computed tomography of head.
   C. Magnetic resonance imaging of head.
   D. Measurement of hemoglobin S percentage.
   E. Transcranial Doppler ultrasonography.

5. A 15-year-old boy with sickle cell disease (genotype SS) has had several vaso-occlusive crises. Which of the following statements after treatment with hydroxyurea for this patient is most accurate?

   A. Baseline hemoglobin level will be lower.
   B. Cellular DNA repair mechanisms are impaired.
   C. Increased circulating neutrophil numbers will offer protection against bacterial infection.
   D. Increased expression of fetal hemoglobin will occur.
   E. Transcranial Doppler velocities will increase.

Condolences

The staff of *Pediatrics in Review* has lost another special colleague and friend. Dr. Gregory Liptak, a skilled and compassionate developmental pediatrician and member of our Editorial Board, died on March 3, 2012, and will be missed by all of us.

Sickle Cell Disease

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