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Section on Hematology/Oncology

Committee on Genetics

Health Supervision for Children With Sickle Cell Disease

ABSTRACT. Sickle cell disease (SCD) is a group of complex genetic disorders with multisystem manifestations. This statement provides pediatricians in primary care and subspecialty practice with an overview of the genetics, diagnosis, clinical manifestations, and treatment of SCD. Specialized comprehensive medical care decreases morbidity and mortality during childhood. The provision of comprehensive care is a time-intensive endeavor that includes ongoing patient and family education, periodic comprehensive evaluations and other disease-specific health maintenance services, psychosocial care, and genetic counseling. Timely and appropriate treatment of acute illness is critical, because life-threatening complications develop rapidly. It is essential that every child with SCD receive comprehensive care that is coordinated through a medical home with appropriate expertise.

ABBREVIATIONS. SCD, sickle cell disease; HbS, sickle hemoglobin; HbF, fetal hemoglobin; HbSS, sickle cell anemia; HbSC, sickle-hemoglobin C disease; HbF, fetal hemoglobin; HPLC, high-performance liquid chromatography; AAP, American Academy of Pediatrics; CNS, central nervous system; CBC, complete blood cell; TCD, transcranial Doppler; HbA_2, hemoglobin A_2; MCV, mean corpuscular volume; Hib, *Haemophilus influenzae* type b; TIA, transient ischemic attack.

INTRODUCTION

The term sickle cell disease (SCD) describes a group of complex, chronic disorders characterized by hemolysis, unpredictable acute complications that can rapidly become life-threatening, and the variable development of chronic organ damage. Expert, comprehensive medical care decreases morbidity and prolongs life expectancy for individuals with SCD.[1–5] Many children with SCD in the United States receive much of their medical care from pediatricians. This statement is intended to provide pediatricians in primary care and subspecialty practice with an overview of the essential components of comprehensive care for children with SCD and their families. A detailed discussion of the treatment of individual acute and chronic complications of SCD is beyond the scope of these guidelines but is available elsewhere.[6–11]

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

OVERVIEW OF GENETICS AND PATHOPHYSIOLOGY

SCD is an autosomal recessive genetic disorder characterized by the presence of sickle hemoglobin (HbS) in red blood cells. Heterozygous individuals have sickle cell trait, a generally benign, asymptomatic genetic carrier state. Homozygous and compound heterozygous individuals have symptomatic disease. Four genotypes—sickle cell anemia (HbSS), sickle-hemoglobin C disease (HbSC), and 2 types of sickle β-thalassemia ($S\beta^+$-thalassemia and $S\beta^o$-thalassemia)—account for most SCD in the United States. Less common forms of SCD are caused by coinheritance of HbS with other hemoglobin variants, such as hemoglobin D-Punjab. Genes for SCD are common in persons of African, Mediterranean, Middle Eastern, and Indian ancestry and persons from the Caribbean and parts of Central and South America. SCD is the most prevalent disorder identified by neonatal blood screening, with approximately 2000 affected infants born in the United States each year.[12] Overall, the incidence of SCD exceeds that of most other serious genetic disorders, including cystic fibrosis and hemophilia.

The protean clinical manifestations of SCD result from variable degrees of hemolysis and intermittent episodes of vascular occlusion that cause tissue ischemia and acute and chronic organ dysfunction. Consequences of hemolysis may include chronic anemia, jaundice, predisposition to aplastic crisis, cholelithiasis, and delayed growth and sexual maturation. Vaso-occlusion and tissue ischemia can result in acute and chronic injury to virtually every organ of the body. Important clinical manifestations of SCD during childhood and adolescence are shown in Table 1. Generally, children with HbSS and $S\beta^o$-thalassemia are more severely affected than are children with HbSC or $S\beta^+$-thalassemia. However, each genotype is characterized by marked and largely unpredictable variability in clinical expression and severity.[13–16]

NEONATAL SCREENING AND DIAGNOSIS

Most infants with SCD are healthy at birth and become symptomatic later in infancy or childhood after fetal hemoglobin (HbF) levels decrease. Most infants with SCD born in the United States are now identified by routine neonatal screening.[9,17,18] Affected infants not identified through neonatal screening generally present clinically during infancy or early childhood with painful swelling of the hands

TABLE 1. Important Clinical Manifestations of SCD During Childhood and Adolescence

Acute Manifestations
Bacterial sepsis or meningitis*
Recurrent vaso-occlusive pain (dactylitis, musculoskeletal or abdominal pain)
Splenic sequestration*
Aplastic crisis*
Acute chest syndrome*
Stroke*
Priapism
Hematuria, including papillary necrosis
Chronic manifestations
Anemia
Jaundice
Splenomegaly
Functional asplenia
Cardiomegaly and functional murmurs
Hyposthenuria and enuresis
Proteinuria
Cholelithiasis
Delayed growth and sexual maturation
Restrictive lung disease*
Pulmonary hypertension*
Avascular necrosis
Proliferative retinopathy
Leg ulcers
Transfusional hemosiderosis*

* Potential cause of mortality.

and feet (dactylitis), pneumococcal sepsis or meningitis, severe anemia and acute splenic enlargement (splenic sequestration), acute chest syndrome, pallor, jaundice, or splenomegaly. Clinical presentations in older children include anemia, severe or recurrent musculoskeletal or abdominal pain, aplastic crisis, acute chest syndrome, splenomegaly or splenic sequestration, and cholelithiasis.

Forty-four states, the District of Columbia, Puerto Rico, and the Virgin Islands currently provide universal neonatal screening for SCD; screening is available by request in the other 6 states. It is essential that pediatricians be familiar with their particular state's screening program, that a screening sample always be obtained before any blood transfusion (regardless of gestational or postnatal age),[19] and that the results of neonatal screening tests be routinely and promptly documented for all infants.[18] In states that have not yet implemented universal screening, neonatal screening for SCD should be requested for all high-risk infants (those of African, Mediterranean, Middle Eastern, Indian, Caribbean, and Central and South American ancestry). Any high-risk infant not screened at birth, or for whom neonatal screening results cannot be documented, should be screened by hemoglobin electrophoresis as soon as possible after birth. For infants with positive screening results, confirmatory testing should be accomplished before 2 months of age so that parental education, penicillin prophylaxis, and arrangements for comprehensive care can be promptly initiated.[9,18]

Confirmatory testing of infants with positive neonatal screening results and diagnosis of older patients who present with symptoms require hemoglobin separation by electrophoresis (cellulose acetate and citrate agar), isoelectric focusing, and/or high-performance liquid chromatography (HPLC).[18] In selected cases, DNA analysis or testing of parents can be helpful. Neonatal screening and diagnostic test results for the 4 most common genotypes of SCD are shown in Table 2. Solubility testing has no place in the diagnosis of SCD, because it does not differentiate SCD from sickle cell trait and because high levels of HbF cause false-negative results in infants with SCD.

OVERVIEW OF COMPREHENSIVE CARE

SCD is a complex disorder with multisystem manifestations that requires specialized comprehensive care to achieve an optimal outcome. Appropriate treatment requires the active involvement of health care professionals with expertise in the management and treatment of SCD, usually a pediatric hematologist-oncologist working in conjunction with a multidisciplinary team.

TABLE 2. SCD: Neonatal Screening and Diagnostic Test Results

Disorder	Approximate Percentage of US Patients With SCD	Neonatal Screening Results*	Hemoglobin Separation by Age 6 Weeks*	Serial CBC and Reticulocyte Counts	Hematologic Studies by Age 2 Years		
					MCV†	HbA_2‡ (%)	HbF (%)
HbSS	65	FS	FS	Hemolysis and anemia by age 6–12 mo	Normal or increased§	<3.6§	<25
HbSC	25	FSC	FSC	Mild or no anemia by age 2 y	Normal or decreased	NA‖	<15
$S\beta^+$-thalassemia	8	FSA or FS¶	FSA	Mild or no anemia by age 2 y	Normal or decreased	>3.6	<25
$S\beta^\circ$-thalassemia	2	FS	FS	Hemolysis and anemia by age 6–12 mo	Decreased	>3.6	<25

Table shows typical results—exceptions occur. Rare forms of SCD, such as SD-Punjab, SO-Arab, SC-Harlem, $S\delta\beta$-thalassemia, SE, and SLepore, not included.

* Hemoglobins reported in order of quantity (eg, FSA = F>S>A).

† Normal or reference range of MCV is > 70 fL at age 6–12 mo; lower limits of reference range subsequently increase with age to 80 fL during adolescence.

‡ HbA_2 results vary somewhat depending on laboratory methodology.

§ HbSS with coexistent α-thalassemia may show decreased MCV and HbA_2 >3.6%; however, neonatal screening results from such infants usually show Bart's hemoglobin.

‖ NA = not applicable—quantity of HbA_2 usually not measured in presence of HbC.

¶ Quantity of HbA at birth is sometimes insufficient for detection.

Medical Home

It is essential that every child with SCD receive care that is provided and coordinated through an appropriate medical home.[17] For many patients, the most appropriate medical home is a multidisciplinary sickle cell clinic that coordinates all aspects of comprehensive care in collaboration with the child's primary care pediatrician or that provides specialty and primary care in 1 setting. In other cases, the medical home may be provided by a knowledgeable primary care pediatrician or other health care professional from whom patients receive day-to-day care, with periodic referrals to sickle cell specialists for comprehensive evaluations and for the management and treatment of severe, life-threatening complications. Some SCD programs support primary care pediatricians by conducting outreach clinics in communities distant from tertiary care centers. The location of the medical home and the extent to which the care outlined in this statement is provided by the primary care pediatrician versus the multidisciplinary SCD team will vary among patients and communities and will depend in part on the expertise of the primary care pediatrician, access to a multidisciplinary SCD team, family preference, and the frequency and severity of disease manifestations. Appropriate management of many aspects of SCD requires time and expertise beyond levels provided by most primary care pediatricians. In some cases, ongoing access to the pediatric hematologist-oncologist and other subspecialists may require advocacy by the primary care pediatrician with managed care organizations or other payers.[5]

Family and Patient Education

Identification of an infant with SCD through neonatal screening provides an opportunity to educate parents and other caregivers about the child's disorder before symptoms develop.[9,18] Initially, the focus should include the genetics (including the availability of carrier testing and prenatal diagnosis) and basic pathophysiology of SCD and the importance of regularly scheduled health maintenance visits, penicillin prophylaxis, and immunizations, including pneumococcal vaccines. Education about the need for urgent medical evaluation for and treatment of febrile illness, acute splenic sequestration, aplastic crisis, and acute chest syndrome is critical. Education about splenic sequestration includes the need to seek medical attention immediately if the child is pale and listless and instruction about abdominal palpation for determining spleen size. Recognition and appropriate management of dactylitis and other painful events should be reviewed. As the child ages, other topics such as stroke, enuresis, priapism, cholelithiasis, delayed puberty, proliferative retinopathy, avascular necrosis of the hip or shoulder, and leg ulcers are introduced. During middle childhood and adolescence, education is increasingly directed toward the patient in addition to the parents, and during adolescence, it includes the genetic basis of SCD and issues related to contraception, carrier testing of partners, genetic counseling, and prenatal diagnosis. The ultimate goal is to enable families to functionally cope with the child's complex chronic illness and enhance the child's potential for successful transition to adulthood.

Health Maintenance

In addition to ensuring compliance with "Recommendations for Preventive Pediatric Health Care" of the American Academy of Pediatrics (AAP),[20] the following SCD-related issues should be addressed periodically.

Prophylactic Medications

All infants with HbSS and Sβ^o-thalassemia should receive penicillin V potassium prophylaxis, 125 mg orally, twice a day, initiated by 2 months of age.[6,9,21,22] The dose is increased to 250 mg orally, twice a day, at 3 years of age and continued at least until the fifth birthday.[22,23] Erythromycin prophylaxis may be used as an alternative for children with suspected or proven penicillin allergy. The routine use of penicillin prophylaxis for infants and children with HbSC and Sβ^+-thalassemia is controversial.[24] Folic acid supplementation is also controversial.[25]

Immunizations

Timely administration of routine immunizations recommended by the AAP is essential.[26] Children with SCD should receive the 7-valent pneumococcal conjugate and 23-valent pneumococcal polysaccharide vaccines.[22,27] Yearly influenza immunization is recommended.[28] The AAP *2000 Red Book* also recommends immunization with quadrivalent meningococcal polysaccharide vaccine.[28]

Comprehensive Medical Evaluations

All patients should have regularly scheduled comprehensive medical evaluations to review previous disease manifestations, document important baseline physical findings and laboratory values, monitor growth and development, detect early signs of chronic organ damage, and develop individualized patient care plans.[18] Blood pressure should be evaluated in light of the observation that values for persons with SCD are somewhat lower than for hematologically normal individuals.[29] Relatively elevated blood pressures have been associated with an increased risk of stroke and may warrant additional evaluation and treatment.[29] Other potential problems include splenomegaly and the detection and treatment of central nervous system (CNS) disease, proliferative retinopathy, restrictive lung disease, pulmonary hypertension, cholelithiasis, proteinuria, avascular necrosis of the hip or shoulder, and leg ulcers. School performance should be monitored for evidence of neurodevelopmental problems. Comprehensive evaluations also provide an ideal setting for providing age-appropriate family and patient education and for evaluating and addressing psychosocial issues. The frequency of comprehensive evaluations will vary somewhat depending on the patient's age, genotype, and disease manifestations.

Some patients will develop complications or show laboratory or imaging evidence of disease manifes-

tations that warrant more intense, specific therapy, such as chronic transfusions, hydroxyurea, or hematopoietic stem cell transplantation. The usual goal of chronic transfusions is to suppress erythropoiesis and provide normal red blood cells to maintain the percentage of the patient's cells (ie, those containing HbS) at less than 30%.[6,30,31] This approach significantly decreases the risk of recurrent stroke and other SCD-related complications, such as vaso-occlusive pain and acute chest syndrome.[30–32] Strategies for preventing and treating transfusion complications, including alloimmunization to minor red blood cell antigens and hemosiderosis, need to be carefully considered.[6,30,33–37] Daily oral administration of hydroxyurea increases HbF levels, decreases leukocyte counts, and decreases the frequency of episodes of pain and acute chest syndrome.[38] Hydroxyurea may be appropriate for selected children and adolescents with frequent or severe disease manifestations but requires frequent monitoring for myelotoxicity and other drug-related complications by a physician with expertise in SCD and chemotherapy.[39] Successful stem cell transplantation provides a hematologic cure for SCD,[40] but its use has been limited by the paucity of HLA-matched sibling donors and by the challenge of balancing SCD severity criteria with transplantation-related morbidity and mortality.[41] The clinical course of each patient with SCD should be regularly reviewed by a pediatric hematologist-oncologist generally at the time of comprehensive evaluations, and the possibilities of chronic transfusions, hydroxyurea, and stem cell transplantation should be considered.

Acute Illness

Acute illness characterized by relatively common childhood signs and symptoms, such as fever, cough, abdominal pain, pallor, and limp, can rapidly become life-threatening. Unfortunately, delayed or inadequate evaluation and treatment of acute illness remains an important cause of preventable morbidity and mortality.[42] Thus, it is imperative that every child with SCD have a plan for around-the-clock access to a medical facility where knowledge and perspective about SCD is available and where evaluation and treatment can be promptly delivered.[9,18] For example, a child with fever or pallor and listlessness should always be initially evaluated, if possible, at a site where complete blood cell (CBC) and reticulocyte counts, blood cultures, intravenous antibiotics, and red blood cell transfusions are readily available. Health care professionals who treat acute illness need ready access to baseline information about the patient (eg, SCD genotype, the presence or absence of splenomegaly, and baseline CBC and reticulocyte counts). Strategies for ensuring the availability of baseline information about individual patients include computerized patient databases and the provision of baseline information directly to patients and families on medical alert cards or on emergency information forms recommended by the AAP.[43] The goal of ensuring timely medical treatment for acute illness also is facilitated by providing anticipatory guidance to patients and families about early recognition, appropriate medical evaluation, and treatment of common acute complications.[9,18]

Examples of acute illnesses that require urgent evaluation and treatment are outlined briefly below. More than one of these acute complications may be present simultaneously, and the information provided here lacks many important details about the management of each. Additional details are provided in references cited throughout this statement. Because blood transfusions play a central role in the treatment of some acute complications, the patient's red blood cell antigen phenotype should be determined ahead of time if minor antigen-matched red blood cells, selected to prevent alloimmunization, are available locally.[6,30,33–35]

Fever

Because patients with SCD develop splenic dysfunction at as early as 3 months of age, they are at high risk for septicemia and meningitis with pneumococci and other encapsulated bacteria.[44] Thus, all patients with temperature greater than 38.5°C require rapid triage and physical assessment, urgent CBC and reticulocyte counts, blood culture (plus cerebrospinal fluid analysis and other cultures as indicated), and prompt administration of a broad-spectrum parenteral antibiotic, such as ceftriaxone sodium, cefuroxime, or cefotaxime sodium.[6,9,11] Because of its long half-life, ceftriaxone is usually chosen for selected cases in which outpatient management with close follow-up may be appropriate.[45] The presence of a focus of infection (eg, viral upper respiratory illness, otitis media) does not alter the urgency of administering parenteral antibiotics. Because of the prevalence of resistant pneumococci,[46] vancomycin hydrochloride should be added for proven or suspected meningitis and other severe illness. Infections such as osteomyelitis that are often caused by *Staphylococcus aureus* or other organisms, such as *Salmonella* species, should be treated with a broad-spectrum antibiotic and vancomycin pending the results of bacteriologic culture and sensitivities. Other acute complications of SCD, such as acute chest syndrome, splenic sequestration, and aplastic crisis, need to be excluded during febrile illness.

Pain

Unpredictable episodes of severe and sometimes excruciating pain are characteristic of SCD.[16,47] Many uncomplicated episodes of pain can be managed at home with oral fluids; oral analgesics, such as ibuprofen, acetaminophen, and codeine; and comfort measures, such as heating pads. When home management measures fail to adequately alleviate pain, it is essential that patients receive rapid triage, physical assessment, and aggressive, appropriately monitored analgesia.[47] For severe pain, parenteral opioids, such as morphine, are indicated and usually administered by scheduled around-the-clock dosing or patient-controlled analgesia.[6,47] Opioids should not be withheld because of the unfounded fear of addiction. Other issues include maintenance of adequate (but avoidance of excessive) hydration, monitoring of oxygenation and cardiopulmonary status,

use of incentive spirometry to encourage deeper inspiratory effort,[48] and close observation for the development of other complications, particularly acute chest syndrome.[49,50] During episodes of severe pain, life-threatening complications may develop rapidly and often are heralded by relatively sudden clinical changes, such as an increasing oxygen requirement, altered mental status, or decreasing hemoglobin level or platelet count.[49–51]

Acute Chest Syndrome

Acute chest syndrome is an illness characterized by a new infiltrate identified on a chest radiograph, accompanied or preceded by lower respiratory tract symptoms and/or hypoxemia.[49,50] The syndrome may be present initially during an acute illness or may develop after 2 to 3 days of severe vaso-occlusive pain. Acute chest syndrome is also a common complication of general anesthesia and surgery.[52] Causes include infection (viral and bacterial, including *Mycoplasma* or *Chlamydia* species), pulmonary infarction, and pulmonary fat embolism.[50] Patients may deteriorate rapidly with progression to pulmonary failure and death. Early recognition and aggressive treatment with oxygen, analgesics, antibiotics, and often simple or exchange transfusions are essential and may be life saving.[6,30,49,50,53] The availability of a pediatric intensive care unit is critical in some cases.

Splenic Sequestration

Splenic sequestration is an acute illness characterized by an acutely enlarging spleen and hemoglobin level more than 2 g/dL below the patient's baseline value.[6,9] Mild to moderate thrombocytopenia is often present. Severe cases progress rapidly to shock and death. Prompt recognition and treatment with red blood cell transfusions may be life saving.[30] Surgical splenectomy to prevent recurrence is often recommended after recovery from life-threatening or recurrent episodes of sequestration.[6]

Aplastic Crisis

Aplastic crisis is characterized by an exacerbation of the patient's baseline anemia with a substantially decreased reticulocyte count, typically less than 1%.[6,9] Most cases are caused by acute infection with human parvovirus B19, usually without the characteristic rash. Less commonly, parvovirus infection causes other acute complications of SCD that may occur with aplastic crisis, including severe pain, bone marrow necrosis, acute chest syndrome, splenic sequestration, and stroke.[6] Recognition requires comparison of CBC and reticulocyte counts obtained during acute illness with baseline values. Red blood cell transfusions are often needed to prevent heart failure in patients with uncomplicated aplastic crisis or to urgently treat other coexistent complications.[30] Because parvovirus is contagious, isolation from at-risk persons,[28] such as pregnant health care professionals and those with immunodeficiency or chronic hemolysis, and testing of siblings with SCD for concurrent and subsequent aplastic crisis are recommended.

Stroke

Any acute neurologic symptom other than mild headache, even if transient, requires urgent evaluation. Common presenting symptoms and signs of stroke include hemiparesis, aphasia or dysphasia, seizures, monoparesis, severe headache, cranial nerve palsy, stupor, and coma.[54] Initial evaluation includes CBC and reticulocyte counts and noncontrast computed tomography or magnetic resonance imaging to exclude hemorrhage.[6] Red blood cell minor antigen phenotype, if not previously documented, should be determined so that transfusions can be matched to prevent alloimmunization.[29,30,33–35] Magnetic resonance angiography to document large vessel vasculopathy is often performed. Treatment includes anticonvulsants if necessary, other supportive care for seizures or increased intracranial pressure if present, and a program of chronic transfusions, usually initiated acutely by partial exchange transfusion or erythrocytapheresis.[6,30] Ischemic CNS injury can also present with nonfocal or "soft" signs, such as developmental delays or poor school performance.[55] Children at highest risk of stroke can be identified by screening with transcranial Doppler (TCD) ultrasonography.[56] Those with positive findings on TCD ultrasonography may be candidates for primary stroke prevention with chronic transfusions.[57]

Priapism

Priapism is a prolonged painful erection of the penis that commonly occurs in children and adolescents with SCD, often starting during the early morning hours.[58] It occurs in 2 forms: 1) stuttering episodes that last fewer than 2 to 4 hours but are often recurrent and may precede a severe episode, and 2) severe episodes that last more than 2 to 4 hours and may eventually result in impotence. Severe episodes require urgent evaluation and treatment that may include hydration, analgesics, aspiration and irrigation by a urologist, and sometimes blood transfusions.[59]

Psychosocial Care

Comprehensive care includes periodic psychosocial assessments and access to services needed to optimize the patient's and family's adaptation to chronic illness.[6,18] Personal and cultural beliefs about illness and existing stresses and support systems may greatly impact the ability to cope with SCD. Patient support groups and community-based organizations can be important resources. Relevant issues include health insurance coverage, transportation for health care, and education of school personnel about SCD.

GENETIC EDUCATION AND COUNSELING

The pediatrician may be called on to provide education and counseling to a couple at risk of having a child with SCD. In some cases, such couples will be identified by the diagnosis of SCD, sickle cell trait, hemoglobin C trait, or β-thalassemia minor in a previous child. In other cases, couples may be identified

because of ethnic background or previous laboratory testing. It is important that education and genetic counseling be provided by professionals with expertise in genetics and in the clinical manifestations and treatment of SCD.[9,18] The availability of prenatal diagnosis using DNA analysis of samples obtained from chorionic villous sampling or amniocentesis should be discussed. In many cases, referral to a hematologist-oncologist or a clinical geneticist or obstetrician associated with a prenatal diagnosis center is appropriate. The pediatrician may be called on to review the information and to support the family in the decision-making process.

Education and counseling should include review of autosomal recessive inheritance and the provision of accurate information about genetic risk and the clinical course, medical complications, and treatment of the specific SCD genotype relevant to the family. Genetic risk cannot be assumed from the diagnosis of SCD in a previous child or from the family's memory of test results; documentation of adequate parental testing is essential. Such testing includes a CBC count and hemoglobin separation by electrophoresis (cellulose acetate and citrate agar), isoelectric focusing, and/or HPLC.[18] Most individuals with heterozygous β-thalassemia show a decreased mean corpuscular volume (MCV) and increased levels of hemoglobin A_2 (HbA_2) and/or HbF. Thus, accurate quantitation of HbF by alkali denaturation, radial immunodiffusion, or HPLC and of HbA_2 by column chromatography or HPLC is needed if the MCV is decreased or borderline decreased.[18] Solubility testing is inadequate and should never be used for carrier testing, in part because it will not identify individuals with hemoglobin C trait or β-thalassemia. The results of parental testing should be reviewed by an individual with expertise in the diagnosis of hemoglobinopathies.

Adolescents with SCD should receive accurate information about the genetic transmission of SCD and the availability of carrier testing for partners, genetic counseling, and prenatal diagnosis. They should be counseled about avoiding unwanted pregnancies and offered appropriate contraceptive services. When an adolescent with SCD becomes pregnant, comanagement by a hematologist with expertise in SCD and by a high-risk obstetrician is essential. Options for partner testing, genetic counseling, and prenatal diagnosis should be reviewed. Pregnancy is often associated with an increased frequency of complications of SCD, but most appropriately managed pregnancies in women with SCD have a successful outcome for the mother and infant.[60,61]

HEALTH SUPERVISION FROM BIRTH TO 1 YEAR OF AGE: INFANCY

Family Education

1. Review the results of neonatal screening and confirmatory testing (Table 2).
2. Discuss the basic pathophysiology and genetics of SCD, including the availability of carrier testing and prenatal diagnosis.
3. Review the importance of regularly scheduled health maintenance visits, penicillin prophylaxis, and immunizations, including pneumococcal vaccines.
4. Discuss the need for urgent medical evaluation for and treatment with parenteral antibiotics of febrile illness (temperature greater than 38.5°C).
5. Discuss signs and symptoms of acute splenic sequestration and teach abdominal palpation for determining spleen size.
6. Discuss recognition and appropriate management of dactylitis and other painful events.
7. Discuss the significance of respiratory symptoms possibly indicative of acute chest syndrome.
8. Recommend avoidance of exposure to pet reptiles to decrease the risk of salmonellosis.[62]
9. Discuss medical home options (primary care pediatrician vs comprehensive sickle cell program). Stress the need for coordinated care and communication among the family, pediatrician, and subspecialists. The roles and responsibilities of family and providers should be discussed and defined.
10. Provide written materials to reinforce education.

Health Maintenance

1. Begin prophylactic administration of penicillin V potassium, 125 mg orally, twice a day, by 2 months of age for infants with HbSS and Sβ^o-thalassemia.[6,9,21,22,27] The routine use of penicillin prophylaxis for infants with HbSC and Sβ^+-thalassemia is controversial.[24]
2. Provide routine immunizations, including *Haemophilus influenzae* type b (Hib) and 7-valent pneumococcal conjugate vaccines, beginning at 2 months of age.[22,26–28] Yearly influenza immunization is recommended for children 6 months and older.[28]
3. Provide comprehensive medical evaluations every 2 to 4 months. Critical issues during the first year include the documentation of spleen size and baseline CBC and reticulocyte counts, which may change significantly as HbF levels decrease. Baseline information should be provided to parents. Red blood cell minor antigen phenotype should be determined if transfusions that may be needed for treatment of acute illness can be matched to prevent alloimmunization.[30,34,35] Develop and modify as needed an individualized patient care plan.

Acute Illness

1. Develop a plan for around-the-clock access to a medical facility that can provide urgent evaluation for and treatment of acute illness characterized by fever (temperature greater than 38.5°C), pallor, lethargy, abdominal distention or enlarging spleen size, or tachypnea or other signs of respiratory illness.
2. Arrange immediate access at the acute care facility to baseline information about the patient.
3. Anticipate and address any insurance barriers to the receipt of appropriate care for acute illness.

Psychosocial Care

1. Explore personal beliefs about illness and existing sources of stress and support.
2. Review insurance coverage and provide assistance with application for public support, if applicable.
3. Discuss transportation issues, particularly for episodes of acute illness.
4. Provide information regarding support groups and other community-based organizations.

HEALTH SUPERVISION FROM 1 TO 5 YEARS OF AGE: EARLY CHILDHOOD

Family Education

1. Review disease manifestations to date, if any, and the parents' response.
2. Review the importance of penicillin prophylaxis, if applicable, and of urgent medical evaluation for and treatment of febrile illness (temperature greater than 38.5°C).
3. Review signs, symptoms, and appropriate management of splenic sequestration and other anemic crisis, dactylitis and other manifestations of pain, and acute chest syndrome.
4. Discuss CNS manifestations of SCD and stress the importance of urgent evaluation for signs or symptoms suggestive of stroke or transient ischemic attack (TIA). Discuss screening with TCD ultrasonography, if available.
5. Discuss enuresis and relationship to SCD.
6. Discuss activities, including the need to avoid temperature extremes and to maintain adequate hydration.
7. Recommend avoidance of exposure to pet reptiles to decrease the risk of salmonellosis.[62]
8. Reinforce the rationale and importance of periodic comprehensive evaluations.
9. Reconsider the patient's medical home model depending on family preference and frequency and severity of complications.

Health Maintenance

1. Continue prophylactic administration of penicillin V potassium, 125 mg orally, twice a day, for children with HbSS and Sβ^0-thalassemia.[6,9,21,22,27] At 3 years of age, increase the dosage to 250 mg orally, twice a day.[22,27] The routine use of penicillin prophylaxis for children with HbSC and Sβ^+-thalassemia is controversial.[24]
2. Complete immunization with Hib and 7-valent pneumococcal conjugate vaccines.[22,26–28] Administer the 23-valent pneumococcal polysaccharide vaccine at 2 and 5 years of age but no earlier than 6 to 8 weeks after the last dose of pneumococcal conjugate vaccine.[22,27] Yearly influenza immunization is recommended.[28]
3. Provide comprehensive medical evaluations at least every 6 to 12 months and modify the patient's care plan as needed. Important issues include growth and development; jaundice; sleep apnea; cardiopulmonary status, including systemic hypertension and functional heart murmurs; spleen size; and neurologic status.
4. Document baseline CBC and reticulocyte counts (every 6–12 months for patients with HbSS and Sβ^0-thalassemia and at least yearly for patients with HbSC and Sβ^+-thalassemia).
5. Baseline renal and liver function tests, urinalysis, chest radiography, pulse oximetry, electrocardiography, echocardiography, and/or TCD ultrasonography may be indicated.

Acute Illness

1. Develop a plan for around-the-clock access to a medical facility that can provide urgent evaluation for and treatment of acute illness characterized by fever (temperature greater than 38.5°C), pallor, lethargy, abdominal distention or enlarging spleen size, tachypnea or other signs of respiratory illness, or any neurologic sign or symptom.
2. Arrange immediate access at the acute care facility to baseline information about the patient.
3. Anticipate and address any insurance barriers to the receipt of appropriate care for acute illness.

Psychosocial Care

1. Explore personal beliefs about illness and existing sources of stress and support.
2. Review insurance coverage and provide assistance with application for public support, if applicable.
3. Discuss transportation issues, particularly for episodes of acute illness.
4. Provide information regarding support groups and other community-based organizations.
5. Discuss child care or preschool arrangements and offer to assist in educating child care providers or educators about SCD.

HEALTH SUPERVISION FROM 5 TO 13 YEARS OF AGE: LATE CHILDHOOD

Patient and Family Education

1. Review disease manifestations to date and patient's and family's response.
2. Stress the continued importance of urgent medical evaluation for and treatment of febrile illness (temperature greater than 38.5°C).
3. Review home management of painful events.
4. Reinforce anticipatory guidance regarding anemic crisis (including splenic sequestration for patients with HbSC and Sβ^+-thalassemia), acute chest syndrome, stroke, and TIA. Discuss screening with TCD ultrasonography, if available.
5. For boys, discuss priapism, initial home management, and the need for urgent evaluation for and treatment of prolonged episodes.
6. Discuss enuresis, if applicable, and its relationship to SCD.
7. Discuss issues related to activity, including participation in athletics, avoidance of temperature extremes, and maintenance of hydration.
8. Recommend avoidance of exposure to pet reptiles to decrease the risk of salmonellosis.[62]

9. Reinforce the rationale and importance of periodic comprehensive evaluations.
10. Reconsider the patient's medical home model depending on family preference and frequency and severity of complications.

Health Maintenance

1. Continuation of prophylactic administration of penicillin V potassium, 250 mg orally, twice a day, after the fifth birthday may be appropriate in selected patients, including those with a history of invasive pneumococcal infection or surgical splenectomy.[22,23,27,28]
2. Administer Hib and 7-valent pneumococcal conjugate vaccines if not previously immunized. Administer second 23-valent pneumococcal polysaccharide vaccine at 5 years of age but no earlier than 3 years after the first pneumococcal polysaccharide vaccine and 6 to 8 weeks after the last pneumococcal conjugate vaccine.[22,27] A third dose of pneumococcal polysaccharide vaccine may be given no earlier than 5 years after the second pneumococcal polysaccharide vaccine and 6 to 8 weeks after the last pneumococcal conjugate vaccine. Yearly influenza immunization is recommended.[28]
3. Provide comprehensive medical evaluations every 6 to 12 months and modify the patient's care plan as needed. Important issues include growth and development; sleep apnea; cardiopulmonary status, including systemic hypertension and functional heart murmurs; hepatosplenomegaly; cholelithiasis; proteinuria; pubertal development; enuresis; avascular necrosis of the hip and shoulder; and neurologic status. Screening for proliferative retinopathy with periodic retinal examinations beginning at 10 years of age is often recommended, especially for patients with HbSC.
4. Document baseline CBC and reticulocyte counts at least yearly.
5. Baseline pulse oximetry, renal and hepatic function tests, chest radiography, pulmonary function tests, electrocardiography, echocardiography, and/or TCD ultrasonography may be indicated.
6. Abdominal ultrasonography to detect cholelithiasis may be indicated.

Acute Illness

1. Develop a plan for around-the-clock access to a facility that can provide urgent evaluation for and treatment of acute illness characterized by fever (temperature greater than 38.5°C), pallor, lethargy, abdominal distention or enlarging spleen size, tachypnea or other signs of respiratory illness, prolonged priapism, or any neurologic sign or symptom.
2. Arrange immediate access at the acute care facility to baseline information about the patient.
3. Anticipate and address any insurance barriers to the receipt of appropriate care for acute illness.

Psychosocial Care

1. Explore personal beliefs about illness and existing sources of stress and support.
2. Review insurance coverage and provide assistance with application for public support, if applicable.
3. Discuss transportation issues, particularly for episodes of acute illness.
4. Provide information regarding support groups and other community-based organizations.
5. Review school attendance and performance and consider formal neurocognitive testing.
6. Offer assistance with education of school personnel about SCD.

HEALTH SUPERVISION FROM 13 TO 21 YEARS AND OLDER: ADOLESCENCE TO EARLY ADULTHOOD

Patient and Family Education

1. Review disease manifestations to date and patient's and family's response.
2. Discuss the nature of SCD with the patient and review concerns and issues related to the impact of the disease throughout adolescence.
3. Review principles of pain management.
4. Review need for urgent medical evaluation for and treatment of febrile illness (temperature greater than 38.5°C).
5. Provide anticipatory guidance regarding anemic crisis (including splenic sequestration for HbSC and Sβ^+-thalassemia), acute chest syndrome, stroke, TIA, and priapism.
6. Discuss sexuality and the availability of contraception options, such as barriers, intramuscular medroxyprogesterone, and low-dose estrogen oral contraceptives.
7. Discuss genetics, including partner testing, genetic counseling, and prenatal diagnosis.
8. Discuss issues related to physical activity, including athletics, avoidance of temperature extremes, and maintenance of hydration.
9. Discuss the importance of avoiding drugs, such as alcohol, tobacco, and cocaine, which may precipitate or exacerbate complications of SCD.
10. Discuss chronic manifestations of the disease, including proliferative retinopathy, cholelithiasis, avascular necrosis of the hip and shoulder, leg ulcers, and delayed growth and puberty.
11. Recommend avoidance of exposure to pet reptiles to decrease the risk of salmonellosis.[62]
12. Reinforce rationale and importance of periodic comprehensive evaluations.
13. Reconsider patient's medical home model depending on patient and family preference and frequency and severity of complications.
14. Discuss options for adult-oriented health care providers and develop with the patient a plan for transition from pediatric to adult medical care.

Health Maintenance

1. Yearly influenza immunization is recommended.[28]
2. Provide comprehensive medical evaluations every 6 to 12 months and modify the patient's care

plan as needed. Important issues include adolescent maturation and development; sleep apnea; cardiopulmonary status, including systemic hypertension, restrictive lung disease, and pulmonary hypertension; hepatosplenomegaly; cholelithiasis; proteinuria; pubertal development; avascular necrosis; and neurologic status. Periodic retinal examinations are often recommended, especially for patients with HbSC.
3. Document baseline CBC and reticulocyte counts at least yearly.
4. Baseline pulse oximetry, renal and liver function tests, chest radiography, pulmonary function tests, electrocardiography, and/or echocardiography may be indicated.
5. Abdominal ultrasonography to detect cholelithiasis may be indicated.

Acute Illness

1. Develop a plan for around-the-clock access to a facility that can provide urgent evaluation for and treatment of acute illness characterized by fever (temperature greater than 38.5°C), pallor, lethargy, abdominal distention or enlarging spleen size, tachypnea or other signs of respiratory illness, prolonged priapism, or any neurologic sign or symptom.
2. Arrange immediate access at the acute care facility to baseline information about the patient.
3. Anticipate and address any insurance barriers to the receipt of appropriate care for acute illness.

Psychosocial Care

1. Explore personal beliefs about illness and existing sources of stress and support.
2. Review insurance coverage and provide assistance with application for public support, if applicable.
3. Discuss transportation issues, particularly for episodes of acute illness.
4. Provide information regarding support groups and other community-based organizations.
5. Review school attendance and performance and consider formal neurocognitive testing.
6. Offer assistance with education of school personnel about SCD.
7. Discuss educational and vocational goals.

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