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Health Supervision for Children and Adolescents With Sickle Cell Disease: Clinical Report

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Sickle cell disease (SCD) is a group of complex genetic disorders of hemoglobin with multisystem manifestations. The scope of this clinical report is such that in-depth recommendations for management of all complications is not possible. Rather, the authors present an overview focused on the practical management of children and adolescents with SCD and the complications that are of particular relevance to pediatric primary care providers. References with detailed commentary provide further information. Timely and appropriate treatment of acute illness is critical, because life-threatening complications may develop rapidly. 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, nursing support, psychosocial care, and genetic counseling. Ideally, this care includes comanagement by the pediatrician or other pediatric primary care provider and a team of specialist SCD experts: Hematologist, other pediatric specialists, advanced practice providers, nurse specialists, social workers, patient navigators, and educational liaisons.

INTRODUCTION

Sickle cell disease (SCD) describes a group of complex chronic disorders characterized by hemolysis, unpredictable acute complications that may 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.[1–6] Many children and adolescents with SCD in the United States receive much, if not all, of their medical care from pediatricians and other

abstract

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pediatric primary care providers. This report is intended to provide the pediatric primary care provider with an overview of the essential components of comprehensive care for children and adolescents with SCD and their families regardless of where it occurs, and thus facilitate the comfort of both providers and patients. It represents a literature-based consensus of expert opinion, not a systematic review, with the goal of providing practical guidance, both anticipatory and responses to complications, for care of children and adolescents with SCD. Recent publications detail specific ideal components of comprehensive SCD centers.[6–9]

The sickle gene arose in West Africa 50 000 years ago and persisted because of the protection it may convey against cerebral malaria. It spread by migration and the trade of enslaved persons to North Africa, Italy, Turkey, Greece, India, the Caribbean, and the Americas, and occurs today in descendants from all of these areas. In the western world, SCD has largely been viewed as a disorder of people of color (although it occurs in all racial and ethnic groups), and medical services for this population have been limited by access to care related to socioeconomic inequity, historic underinvestment in research for therapeutic development, and systemic racism.[10,11] Racism, in all its forms, including structural, institutional, personally mediated, and internalized, whether implicit or explicit, negatively impacts medical care, particularly for persons with SCD.[12] Solving these problems will require long-term societal changes, but medical providers can begin by addressing their own approach to persons with SCD. One first step is to stop using the depersonalizing term "sickler" for people with SCD and educating colleagues who do. An additional step is to practice personal mindfulness by recognizing that everyone has biases and acknowledging that the challenges faced by patients may not be evident to a practitioner.[13] This process may be aided by universal screening for social drivers of health to help ensure that patients and families have their concerns heard. In addition, helping all staff members, both clinical and administrative, to become aware of and sensitive to the needs and realities of persons with SCD will help to foster the trust of patients and families that racism has no place in medical care.[10–12,14]

Although more than 98% of children born with SCD will survive to transition to adult care, median life expectancy for someone born with sickle cell anemia (HbSS) in the United States is the fifth decade, 2 decades less than individuals of similar race without SCD, a finding that has not improved substantially in the last 25 years.[2,15–17] Improving equity of care for, and increasing knowledge of how to care for, persons with SCD by all health care providers is the goal of this report.

OVERVIEW OF PATHOPHYSIOLOGY

SCD is an autosomal recessive genetic disorder characterized by the presence of sickle hemoglobin (HbS) in red blood cells. Four genotypes, HbSS, sickle hemoglobin C disease (HbSC), and 2 types of sickle β-thalassemia ($S\beta^+$-thalassemia and $S\beta^0$-thalassemia; determined by the amount of hemoglobin A produced), are the most common. Rare forms of SCD are caused by coinheritance of HbS with other hemoglobin variants, such as hemoglobin D-Punjab, hemoglobin E, or hemoglobin O-Arab. A single amino acid change in the beta globin gene causes polymerization of deoxygenated hemoglobin, leading to sickle or crescent-shaped red blood cells. The sickled red blood cells result in hemolysis and intermittent episodes of vascular occlusion that cause tissue ischemia leading to acute and chronic organ dysfunction. Potential acute and chronic manifestations of SCD during childhood and adolescence are shown in Fig 1. Generally, children with HbSS and $S\beta^0$-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.[18]

DIAGNOSIS AND ESTABLISHMENT OF CARE

Infants with SCD are healthy at birth and develop symptoms early in infancy or childhood as the fetal hemoglobin level declines. All 50 states, the District of Columbia, Puerto Rico, the US Virgin Islands, and the US military have some form of newborn screening (NBS) for hemoglobinopathy capable of making a definitive diagnosis of SCD at birth.[19] Pediatricians and pediatric primary care providers are advised to be familiar with their state screening programs, record the result of the hemoglobinopathy screening test (disease, trait, or normal) in the medical record, educate the family when those results are shared with them, and rediscuss the finding in adolescence and at transition to adult care.[20,21] Depending on local care resources, sometimes the pediatric primary care provider is the only source of care for children with SCD. This document seeks to offer best practice information and provide support to fulfill this role.

Ideally, an NBS finding of SCD results in consultation, and most often referral, to a pediatric SCD center or pediatric hematologist for comprehensive care comanagement, with the first visit occurring before 3 months of age. An NBS finding of trait or disease requires education of the parents regarding the potential future risk of their conceiving a subsequent child with SCD.[22,23] In addition, it is important that the results of testing on previously born siblings, including the presence of sickle cell trait, are reviewed and discussed with the family at diagnosis and with that child at least at school entry, preadolescence, and transition visits (Table 1). If NBS results are not available, particularly for children born outside the United States, adolescents, or

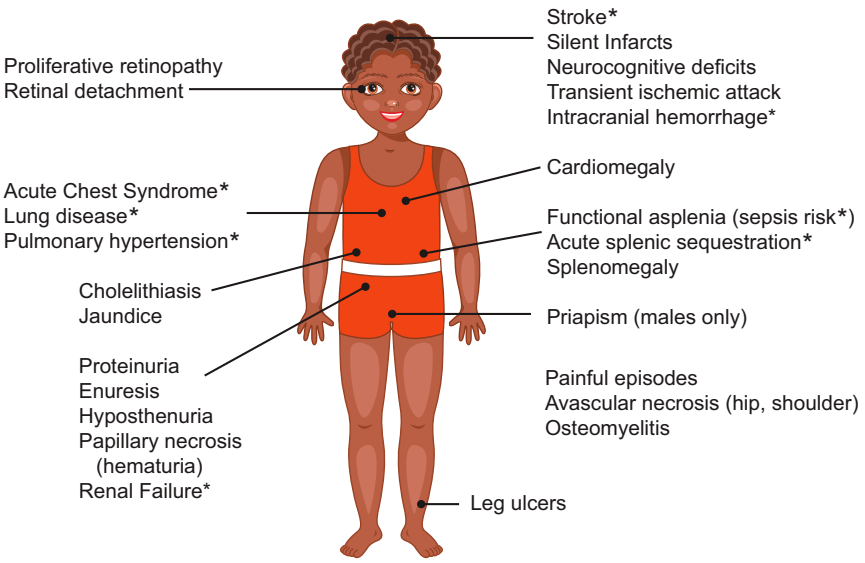

FIGURE 1
Complications of SCD. Additional complications: Anemia, delayed growth, and sexual maturation. * Potential cause of mortality.

patients who transfer into a practice beyond infancy, a hemoglobinopathy evaluation (hemoglobin electrophoresis, high-performance liquid chromatography, isoelectric focusing, or similar testing) is appropriate as soon as possible.[20] If transfusion has occurred, hemoglobinopathy testing is postponed for 3 months, or genetic testing may be performed. Programs like The Innovations in Newborn Screening Interoperability Resource Center and Learning Collaborative, funded by the Health Resources and Services Administration, which seeks to improve data exchange and interoperability between state newborn screening and electronic health record systems, may make locating and sharing this information easier in the future.[24]

COMPLICATIONS OF SICKLE CELL DISEASE

Acute Illness

Acute illness characterized by common childhood signs and symptoms such as fever, cough, abdominal pain, pallor, or a limp, can rapidly become life-threatening in SCD.[1,6] Identification of a medical facility with around-the-clock access to knowledgeable care for evaluation and treatment of SCD is a key component of anticipatory care management for every child with SCD.

Health care professionals who treat acute illness need access to baseline information about the patient (eg, SCD genotype, the presence or absence of splenomegaly, prior splenectomy, chronic complications, usual pulse oximetry values, baseline complete blood cell count [CBC], and reticulocyte counts). Strategies for ensuring the availability of baseline information about individual patients include computerized patient databases and/or the provision of this information directly to patients and families on medical alert cards or on emergency information forms as recommended by the American Academy of Pediatrics.[25] The goal of ensuring timely medical treatment of 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.[6] Examples of acute and chronic complications are outlined briefly below and in Fig 1.[26] More than 1 complication may be present simultaneously.

Red Blood Cell Transfusion

For many acute and chronic complications of SCD, red blood cell transfusion may be required. To minimize the risk of alloimmunization to minor red cell antigens, an extended red blood cell antigen profile, by genotype or serology, is determined prior to the first transfusion and optimally in infancy. Thus, extended, antigen-matched red blood cells (at least for C, E, and Kell antigens) can be transfused when needed.[6,27,28]

Fever

Because patients with SCD may develop splenic dysfunction as early as 3 months of age, they are at high risk for septicemia and meningitis with *Streptococcus pneumoniae* and other encapsulated bacteria.[29] Thus, all children with SCD and a temperature ≥38 to 38.5°C (≥100.4–101.3°F) require rapid triage and examination, urgent CBC and reticulocyte counts, blood culture, and prompt administration of a broad spectrum parenteral antibiotic, such as ceftriaxone sodium.[6,30] Because of its long half-life, ceftriaxone is preferred when outpatient management with close follow-up is planned. Other testing, such as for infection with influenza or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), chest radiographs, and

TABLE 1 Neonatal Screening and Diagnostic Test Results

Disorder	Newborn Screening Results	Hemoglobin Separation Mid-Childhood	Hemoglobin (g/dL) Mid-Childhood	MCV (fL)
HbSS	FS	S	Decreased	Normal to increased
HbSC	FSC	SC	Decreased	Normal
SB^{+}-thalassemia	FSA	SA	Decreased to normal	Decreased
SB^{0}-thalassemia	FS	S	Decreased	Decreased
S trait	FAS	AS	Normal	Normal

Table shows typical results; exceptions occur. Hemoglobins are reported in order of quantity (eg, FSA = F>S>A).

cerebrospinal fluid or urine cultures are obtained only for standard clinical indications. The presence of a focus of infection (eg, viral upper respiratory illness, otitis media, coronavirus disease 2019/SARS-CoV-2) or prior receipt of immunizations does not alter the urgency of and need for administering parenteral antibiotics. Vancomycin hydrochloride may be added for suspected meningitis and/or sepsis, based on local susceptibility patterns. Infections such as osteomyelitis, often caused by *Staphylococcus aureus* and *Salmonella* species, are initially treated with a broad-spectrum antibiotic and vancomycin pending the results of culture and sensitivities. Other acute complications of SCD, such as acute chest syndrome, splenic sequestration, and transient aplastic crisis, also need to be evaluated for during febrile illness.

Pain

Unpredictable episodes of severe and sometimes excruciating pain are the hallmark of SCD.[31,32] Many uncomplicated episodes of pain can be managed at home with oral fluids, rest, heat, oral analgesics (using full doses of both mild opioid and nonsteroidal antiinflammatory medications, as per their pharmacology), comfort measures, and distraction. Nonpharmacologic methods of pain control, taught to the patient and family previously, are reinforced during the acute pain event.[33] When home management measures fail to adequately manage pain, it is essential that patients receive rapid triage, assessment, and aggressive, appropriately monitored parenteral analgesia in medical facilities. For severe pain, parenteral opioids, such as morphine, are indicated and administered by scheduled around-the-clock dosing or patient-controlled analgesia.[6,32–34] Other issues include adequate maintenance of (but avoidance of excessive) hydration, monitoring of oxygenation and cardiorespiratory status, use of incentive spirometry to encourage deep inspiratory effort,[35] and close observation for the development of other complications, particularly acute chest syndrome.[36] During episodes of severe pain, additional life-threatening complications may develop rapidly and often are heralded by a suddenly increasing oxygen requirement, altered mental status, or declining hemoglobin level or platelet count.[37] It is important to note that transfusion is of no acute benefit for resolution of painful episodes.

Patients are particularly at risk for discrimination in analgesic management of the severe, recurrent, and sometimes chronic pain that occurs in SCD. Because there are rarely any objective physical findings with or identifiable "cause" of even severe pain, persons with SCD may be stigmatized when seeking pain relief.[11,12] Delays in addressing, and undertreatment of, SCD pain are common. Further, studies have documented disparities in pain management between racial groups, with children of color receiving less pain medication for appendicitis or fractures, as well as later recognition of sepsis and fewer antibiotics for equivalent infections.[38–41] If pain is present, it is to be treated aggressively, and, if possible, according to a predetermined personalized analgesic plan of care. In SCD, the children and their caregivers know their disease best, and as far as possible, all actions should be the result of shared decision-making by patient, family, and the health care team. Pediatric providers should work to foster the trust of their patients that they will be heard, particularly when in pain. These efforts will help to ensure the provision of optimal care, and work to mitigate the effects of systemic racism, which causes families to mistrust the health care system, leading to children with SCD being less likely to adhere to best care practices.[10,42–44]

Acute Chest Syndrome

Acute chest syndrome is a life-threatening complication characterized by a new segmental infiltrate identified on a chest radiograph (which may not be visible on first presentation), accompanied by lower respiratory tract symptoms, chest pain, and/or hypoxemia.[36,45] Acute chest syndrome can present acutely or after initial presentation for a pain event and with or without fever. Children with SCD and reactive airway disease have an increased incidence of acute chest syndrome.[46] Acute chest syndrome is also a potential complication following general anesthesia related to hypoventilation (often related to inadequately treated thoracoabdominal pain) and reduced inspiratory effort. Other specific causative factors of acute chest syndrome may include infection (viral, bacterial, *Mycoplasma*, or *Chlamydia*), pulmonary infarction, and pulmonary fat embolism. Patients may deteriorate rapidly with progression to pulmonary failure and death. Early recognition and aggressive treatment with oxygen, incentive spirometry, analgesics, antibiotics, and often, simple or exchange transfusions, may be

lifesaving.[36,45] Red blood cell transfusion, oxygen, or ventilatory support in a PICU may be required.

Splenic Sequestration

Splenic sequestration is an acute illness characterized by a rapidly enlarging spleen and a decrease in hemoglobin level of more than 2 g/dL below the patient's baseline value.[6] Mild to moderate thrombocytopenia is often present. Severe cases may rapidly progress to shock and death. Prompt recognition and careful administration of red blood cell transfusions, when appropriate, may be lifesaving.[47–49] Care must be taken to avoid acute overtransfusion to a hemoglobin greater than 10 g/dL, as sequestered red cells may be acutely released from the spleen as the acute event resolves. Practically, transfusions of 3 to 5 mg/kg are used, and a posttransfusion hemoglobin is checked before the next aliquot of red cells is ordered. Although splenic sequestration is most common in children with HbSS younger than 5 years and adolescents with HbSC, it may occur at any age in patients with any form of SCD. Parents and caregivers of young children with SCD are taught to check their child's spleen daily so they recognize enlargement early and urgently seek medical attention.[50] Surgical splenectomy to prevent recurrence may be recommended after recovery from life-threatening or recurrent episodes.[6]

Transient Aplastic Crisis

Transient aplastic crisis is characterized by an exacerbation of the patient's baseline anemia with a substantially decreased reticulocyte count, typically to below 1%.[6] Recognition requires comparison of CBC and reticulocyte counts obtained during acute illness with baseline values. Red blood cell transfusions are often needed. Acute infection with human parvovirus B19, usually without the characteristic rash, is the most common cause.[51] Parvovirus is highly contagious, so isolation of suspected cases from at-risk persons, such as pregnant health care professionals or others with chronic hemolysis, is recommended.[52] Siblings and others with SCD in contact with the patient are also at risk for concurrent or subsequent aplastic crisis, and a hemoglobin and reticulocyte count is checked.

Stroke

Any acute neurologic symptom other than transient mild headache requires urgent evaluation.[53,54] Common presenting symptoms and signs of stroke include hemiparesis, aphasia or dysphasia, seizures, monoparesis, severe headache, cranial nerve palsy, stupor, and coma. Initial evaluation includes a CBC, reticulocyte count, blood type and crossmatch, and noncontrast computed tomography or MRI of the brain to exclude hemorrhage.[6,54,55] Acute treatment may include partial exchange transfusion or erythrocytapheresis (red cell exchange transfusion) to reduce HbS to <30% and raise hemoglobin to 10 g/dL. MRI, including diffusion-weighted imaging and magnetic resonance angiography (MRA), are used to characterize the stroke and determine whether large vessel vasculopathy is present. After a stroke, a lifelong chronic transfusion program for secondary stroke prevention is recommended.[6,56,57]

To identify children with HbSS or sickle β^0-thalassemia at highest risk of stroke, transcranial Doppler ultrasonography screening is performed yearly between 2 and 16 years of age.[6,53,54] Elevated velocity may indicate a need to initiate a chronic blood transfusion program for primary stroke prevention.[57,58] After at least 1 year of chronic transfusion, a select group of children whose velocities have normalized may transition to hydroxyurea therapy.[59,60] Silent ischemic injury can also occur in SCD and children may present with subtle findings such as developmental delay or poor school performance. MRI/MRA is required to detect such events.[54,61] (See also section on Comprehensive Medical Evaluation below.)

Kidney

Loss of renal concentrating ability (hyposthenuria) affects many persons with SCD starting in infancy and may lead to prolonged issues with enuresis. Fluid restriction may lead to dehydration and, thus, promote intravascular sickling with an increase in painful events. Management includes supportive counseling about the cause of enuresis (related to urinary concentrating deficit of SCD and not behavioral), timed overnight waking to void, and waterproof mattress covers.[62] Renal papillary necrosis presents with painless macroscopic (gross) hematuria attributable to infarction of the renal papillae. Evaluation includes urinalysis, urine culture, abdominal ultrasonography, and screening coagulation tests. Treatment is usually bed rest and hydration. Proteinuria may develop in later childhood or adolescence and may progress to renal insufficiency. Annual screening for elevated urinary protein, by protein (albumin)-to-creatinine ratio, begins by age 10.[6] If repeatedly elevated, screening of first morning voided urine sample for elevated protein-to-creatine ratio and referral to nephrology is advised.[63]

Priapism

Priapism is a prolonged painful erection that commonly occurs in children and adolescents with SCD, often starting during the early morning hours.[64,65] It occurs in 2 forms:

1. stuttering episodes that typically last <4 hours but are often recurrent; and
2. severe acute ischemic episodes that last ≥4 hours and may eventually result in impotence.

Priapism is treated as a painful event with hydration and analgesia, often at home, unless it lasts more than 4 hours, when irreversible tissue damage may start to

occur. Severe acute episodes with a continued erection ≥4 hours require emergent medical evaluation, including urgent urologic consultation, and may require penile aspiration and irrigation in addition to intravenous hydration and analgesia, including opioids, for relief.[66,67]

CHRONIC MANIFESTATIONS

Many potential chronic manifestations of SCD are also shown in Fig 1.[26,68] It is important to note that the anemia that may occur in conjunction with SCD will not improve with iron supplementation. Medicinal iron is not given unless iron deficiency is biochemically proven because of the potential risk of lifetime iron overload from repeated red blood cell transfusions. Pica is common, but is not related to iron status in SCD. Splenomegaly may become chronic and require splenectomy. Cardiomegaly may occur. Evaluation for gallstones may be indicated for a child with SCD and right upper quadrant pain, frequent episodes of vomiting, and/or worsening jaundice. Children with SCD have a higher incidence of obstructive lung disease, which may become restrictive as they get older. Pulmonary hypertension more frequently occurs in adults but may present during childhood. Avascular necrosis of hips or shoulders is common. Proliferative retinopathy, which may lead to retinal detachment, is possible in all types of SCD but especially persons with HbSC.[69] Poorly healing ulcers, especially around the ankles, may require the assistance of a wound care expert. Even in the absence of overt or silent stroke, children with SCD may have neuropsychologic impairment that impacts school and job performance.[54,70]

REVIEW OF CARE

Overview of Comprehensive Care and Comanagement

SCD is a complex disorder with multisystem manifestations requiring comprehensive care from both a pediatrician or other pediatric primary care provider and a multidisciplinary SCD clinic team.[14] Ideally, the pediatric primary care provider manages all aspects of general pediatric care[71] and comanages SCD-specific manifestations (complications) with the SCD team.[7–9] The patient and family are involved in all decisions, including where care occurs. Similar to other chronic illnesses, age, socioeconomic status, and medical/neurobehavioral comorbidities negatively affect health-related quality of life. Thus, for persons with SCD, racial bias complicates all care.[43,72,73]

SCD-specific care, as outlined by a National Institutes of Health consensus statement and expert opinion, may require equipment and resources not available in many pediatric primary care settings.[6,73] The extent to which the comprehensive care outlined in this report is delivered by pediatric primary care practices versus a multidisciplinary specialist sickle cell clinic will vary by community and will depend on the comfort of the primary care provider, availability of local resources, preferences of the family, as well as the frequency and severity of SCD manifestations. However, at least an annual consultation with a multidisciplinary SCD team is strongly advised. Remote virtual visit programs involving the pediatric primary care provider and SCD specialist may be available. Some SCD programs support primary pediatric care providers by conducting outreach clinics in communities distant from tertiary care centers, with available telephone consultation for acute issues.[7,9,74] Regardless, ideally, ongoing close consultation between the pediatric primary care provider and SCD specialist, with a clear delineation of health maintenance responsibilities (to avoid duplication) and rapid access to tertiary care facilities in the event of severe complications, is ideal. In some cases, pediatric primary care providers may need to advocate with managed care organizations or other payers for patients to have access to the SCD team, pediatric hematologist, and other subspecialists.

Patient and Family Education

NBS for hemoglobinopathies supports a diagnosis of SCD before symptoms develop and provides the opportunity for education to allow for a reduction in early complications and mortality. The focus of initial education includes the genetics of the disorder (including that SCD will not go away, trait status of parents and siblings, and availability of prenatal diagnosis, including assisted reproductive technologies for subsequent pregnancies), basic pathophysiology of SCD, and the importance of regularly scheduled general and SCD-specific health care maintenance visits. The rationale for penicillin prophylaxis and immunizations (including additional pneumococcal and meningococcal vaccines) is based on the specific diagnosis. It is key that education about and planning for (including location and how to access) urgent medical evaluation for febrile illness (potential bacteremia), pallor (potential exaggerated or accelerated anemia due to hyperhemolysis or acute splenic sequestration, transient aplastic crisis), and/or difficulty breathing (potential severe anemia, acute chest syndrome) be developed early and reviewed at each visit. A significant component of the education concerns the specific SCD diagnosis (HbSS, HbSC, Sβ^0-thalassemia, or Sβ^+-thalassemia) and the unique spectrum of complications most common to that disorder.

In adolescence, the focus of the education changes from the family to the patient; addressing general SCD education, past personal complications, management of acute problems, use of nonpharmacologic pain management approaches, as well as potential organ dysfunction and the importance of regular medical follow-up. Painful events appear to be more common around menstruation, and education about distinguishing dysmenorrhea from generalized

sickle cell pain may be helpful.[75,76] Genetic counseling and carrier testing of partners; prenatal diagnosis; assisted reproductive technologies, including in vitro fertilization with preimplantation genetic testing; contraception; as well as education, career, and insurance issues for adulthood are also discussed. The goal is to aid the patient and family in recognizing that SCD is a treatable condition that requires attention and active management to achieve optimum life outcomes. Peer education and role models are invaluable for successful adolescent transition to adulthood; patient and family engagement with community-based organizations and online support groups should be encouraged.

HEALTH MAINTENANCE

Comprehensive Medical Evaluations

A sickle cell comprehensive visit includes assessment of hematologic values, review of prior disease manifestations, and physical examination with emphasis on growth and general, as well as neurologic, development. Blood pressure values are carefully reviewed according to age-specific norms, given that values for persons with SCD may be lower than hematologically normal individuals.[6,77,78] Oxygen saturation is evaluated noninvasively and tracked over time. The presence of a palpable spleen is determined and family member education about home daily spleen palpation is reinforced. School performance is monitored by parents, teachers, and all members of the health care team (both generalist and specialist).[14] If academic or neurodevelopmental problems are suspected, assessment including brain MRI/MRA for silent cerebral lesions (common in HbSS) and neurocognitive testing may be warranted.[54] Assistance will be needed in pursuing available educational accommodations such as a 504 plan and/or an individualized education program, to optimize learning. For preschool-aged children with developmental delay, referral to local early childhood intervention programs is indicated.[79]

Age-specific screening for disease complications is a component at all SCD comprehensive visits: For example, stroke risk evaluated by transcranial Doppler ultrasonography in HbSS and Sβ^0-thalassemia starting at age 2, as well as dilated fundoscopic examination for retinopathy and urinary protein evaluations annually starting at age 10 years, for persons with all genotypes.[6] Some groups have recommended a single, nonsedated MRI of the brain for early school-aged children, because poor academic performance may not be a sensitive or specific indicator of SCD-related brain events.[54,61] Imaging will ideally occur using the published parameters for silent cerebral infarct and interpreted by neuroradiologists familiar with the cerebrovascular manifestations of SCD.

If recurrent or persistent pain is an issue, consultation with palliative care or physical medicine services is valuable. This is also a good opportunity to again review interventions to ameliorate SCD (eg, hydroxyurea and other medications, hematopoietic stem cell transplantation or gene therapy, or chronic transfusion), with specific reference to an individual child and their disease course. If the patient is on disease-modifying therapy, adherence is reviewed, as well.

Immunizations

All routine childhood immunizations, including the pneumococcal conjugate vaccine (PCV) series, SARS-CoV-2, and annual inactivated influenza vaccine, as recommended by the American Academy of Pediatrics, are essential, because persons with SCD are considered to be at high risk because of functional asplenia.[80] However, the extent of splenic dysfunction in the absence of surgical splenectomy varies by genotype (with HbSS and HbSβ^0-thalassemia having the earliest and most profound splenic dysfunction). The 2023 recommendations of the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) are a complete PCV series (using either 15-valent [PCV15] or 20-valent [PCV20]) for children with all forms of SCD, with catch-up dosing through 71 months of age. For children 6 to 18 years of age who received all recommended doses of PCV before age 6 years (including at least 1 dose of PCV20), no additional doses of any pneumococcal vaccine are indicated. If no dose of PCV20 was received (all prior doses being 13-valent PCV or PCV15), 1 additional dose of PCV20 or 23-valent pneumococcal polysaccharide vaccine is recommended. For children 6 to 18 years of age with SCD who have not received any doses of PCV (13-valent PCV, PCV15, or PCV20), a single dose of PCV15 or PCV20 is recommended. If PCV15 is used, it should be followed by a dose of 23-valent pneumococcal polysaccharide vaccine at least 8 weeks later (if pneumococcal polysaccharide vaccine has not been previously given).[81] As recommendations for PCV use are evolving rapidly because of introduction of newer vaccines, it is always advisable to consult the relevant sections of the *Red Book* and the most up-to-date immunization schedule.[82–85] The CDC offers PneumoRecs VaxAdvisor, a free customizable vaccination recommendation app that is useful in confirming the vaccines a partially immunized patient may require.[84] Meningococcal conjugate vaccine is given at a young age against serotypes A, C, W, and Y and after age 10 years for serotype B, per recommendations for children with functional asplenia with subsequent boosters.[80,82,86] Current recommendations for timing of all vaccines should be consulted before administration.[82,83]

Prophylactic Medications

Penicillin V potassium prophylaxis, 125 mg orally, twice a day, by 2 months of age, is indicated for all infants with HbSS and Sβ^0-thalassemia. The dose is increased to 250 mg orally, twice a day, at 3 years of age and continued until age 5 years or the pneumococcal vaccine series is completed.[80,82,83,85] Continuation of prophylactic penicillin V after the fifth birthday may be appropriate in selected patients, including those with a history of invasive pneumococcal infection or surgical splenectomy.[23,29,80,85] Routine penicillin prophylaxis for children with HbSC and Sβ^+-thalassemia, in the absence of surgical splenectomy, is not generally recommended.[6,80,87,88] Amoxicillin, 20 mg/kg/day, is sometimes substituted for penicillin based on medication cost or taste,[80] although crushed penicillin tablets given in a small volume of liquid may offer an advantage in terms of cost and the need for biweekly refills.[6] An alternative for children with penicillin allergy is erythromycin. Adherence with, and the rationale for, antibiotic prophylaxis is reviewed at every medical contact. Folic acid supplementation, given the widespread supplementation of formula and grain products in the western world, is no longer needed.[6,89]

Disease-Specific Treatments

In addition to prophylactic penicillin, there are SCD-specific treatments aimed at either modifying or curing the disease. Hydroxyurea is the first agent recommended and the one with which there is the greatest length of experience, particularly in children. In time, a multiagent approach will likely become more common.[90] Hydroxyurea increases total and fetal hemoglobin and decreases vaso-occlusive complications including episodes of painful events and acute chest syndrome, hospitalizations, and need for transfusion.[91,92] The National Heart, Lung, and Blood Institute-funded Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) demonstrated that hydroxyurea is of significant benefit presymptomatically to infants with HbSS or Sβ^0-thalassemia and has no unique adverse effects, even if initiated in early infancy and continued for more than a decade.[93,94] Hydroxyurea use has a positive impact on health-related quality of life in people with HbSS or Sβ^0-thalassemia.[72] The 2014 National Heart, Lung, and Blood Institute guidelines for SCD recommend offering hydroxyurea to every child with HbSS or Sβ^0-thalassemia at 9 months of age even without clinical symptoms.[6] Hydroxyurea is taken once a day orally and is supplied as a capsule, fast-dissolving tablet, or compounded liquid. Myelosuppression is a potential adverse effect; a CBC and reticulocyte count is monitored every 1 to 3 months depending on how long the child has been taking the medication and whether the child has attained a stable dose.[6]

L-glutamine (Endari)* may reduce the number of pain events in children 5 years and older.[95] The mechanism of action is poorly understood, but L-glutamine may regulate nicotinamide adenine dinucleotide + hydrogen/total nicotinamide adenine dinucleotide in red blood cells, decreasing the oxidative stress and, thus, hemolysis. It comes as a powder packet that is mixed in liquid or food twice daily. It does not require laboratory monitoring.

Crizanlizumab, a monoclonal antibody P-selectin inhibitor, blocks adhesion of blood elements to endothelial cells and thus may decrease vaso-occlusion. It is approved for persons 16 years of age and older to decrease the frequency of hospitalization for painful events.[96] It is administered as an intravenous infusion every 4 weeks after two infusions two weeks apart.

Voxelotor, an HbS polymerization inhibitor, increases the affinity of hemoglobin for oxygen and thus decreases HbS polymerization. This results in a mean 1 g increase in hemoglobin.[97] It is approved for children and adults 4 years and older. It is a tablet, or tablet for oral suspension, taken orally once daily.

To prevent the development of some complications of SCD, monthly red blood cell transfusions may be given to suppress the bone marrow and decrease HbS percentage.[27,28] Transfusion is most commonly prescribed for children who are at high risk of developing stroke or who have already developed a stroke (primary or secondary stroke prophylaxis).[6,57–59] Transfusion is also prescribed for select children with recurrent complications who do not respond to other disease-modifying therapies. The potential adverse effects include febrile and allergic reactions, transmission of pathogens, alloimmunization, and iron overload. In addition, some children may require an indwelling central line, which has an associated risk of infection and thrombosis.[6,27,28] After 12 to 20 transfusions, children will require iron chelation therapy to treat iron overload.

Hematopoietic stem cell transplantation has been used as a curative treatment of SCD for almost 4 decades. Best outcomes are achieved when the donor is an HLA-matched sibling and the procedure occurs before 16 years of age.[98,99] Because many patients lack an HLA-matched sibling, alternative donors have been used but have been limited by adverse effects. The main adverse effects include infection, graft rejection, and graft-versus-host disease. Infertility is also a risk, especially with myeloablative transplant regimens.

SCD is a single-gene disorder, making it an ideal candidate for gene therapy. Ongoing clinical research is studying 3 different approaches: (1) gene addition, (2) gene correction,

*Endari is the only formulation of L-glutamine approved by the US Food and Drug Administration for the reduction of pain events in people with SCD. This is not an endorsement by the American Academy of Pediatrics.

TABLE 2 Health Maintenance for Children With Sickle Cell Disease by Age

Frequency of visits	Birth to 12 mo: An SCD-focused visit, in addition to routine scheduled infant health care visits, every 2 to 4 mo Y 1 to 21: An SCD-focused visit, in addition to routine age-appropriate health care visits, at least every 6 to 12 mo; modify to patient's care plan				
All visits	Review disease manifestations to date, and the parent or caregiver's response. In adolescence, review patient's response and understanding. After 1 y of age: Establish baseline blood pressure, respiratory rate, pulse oximetry, and heart rate and document at each visit. Document CBC and reticulocyte count (every 6–12 mo for patients with HbSS and Sβ^0-thalassemia and at least yearly for patients with HbSC and Sβ^+-thalassemia). Provide routine immunizations and immunizations for children with functional asplenia.[80–88] Ensure a plan for around-the-clock access to a facility that can provide urgent evaluation for and treatment of acute illness characterized by fever (preagreed temperature ≥38–38.5°C, pallor, lethargy, abdominal distention, enlarging spleen size, tachypnea, other signs of significant respiratory illness, prolonged priapism, or any neurologic sign or symptom). Arrange immediate access at the acute care facility to SCD-specific baseline information. If patient requires transfusion, red blood cells are matched for extended blood antigens (at least C, E, Kell).[6,27] Explore caregiver personal beliefs about illness and sources of stress and support. Review insurance coverage and provide assistance with application for public support, if applicable. Anticipate and address any insurance barriers to the receipt of appropriate care. Discuss transportation plan, particularly for episodes of acute illness. Provide information regarding support groups and other community-based organizations. Reinforce the rationale and importance of periodic comprehensive evaluations and adherence with urgent evaluation recommendations. Develop and modify individualized patient care plan.				
Health maintenance	Birth–12 mo	Y 1–4	Y 5–12	Y 13–17	Y 18–21
Infection	Prophylactic administration of penicillin V potassium, 125 mg orally, twice a day, by 2 mo of age for infants with HbSS and Sβ^0-thalassemia[a] [6,80,85] Increase the dosage to 250 mg orally, twice a day, at age 3.[a] [6,85]		Discontinue prophylactic penicillin after pneumococcal vaccine series is complete. 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.[23,29,80,85]		
History and physical examination	Growth and development; spleen size, including teaching caregiver home palpation	Growth and development; jaundice; sleep apnea; spleen size; neurologic status; cardiopulmonary status, including systemic hypertension and functional heart murmurs; enuresis	Growth and development, jaundice; sleep apnea; neurologic status; cardiopulmonary status, including systemic hypertension and functional heart murmurs; hepatosplenomegaly, cholelithiasis; proteinuria, enuresis; pubertal development; avascular necrosis of the hip and shoulder	Adolescent maturation and development, puberty; sleep apnea; cardiopulmonary status, including systemic hypertension; restrictive lung disease, pulmonary hypertension; hepatosplenomegaly, cholelithiasis; proteinuria; avascular necrosis of hip and shoulder; neurologic status	
Additional testing	Red blood cell minor antigen typing (at least C, E, Kell)[6,27]	—	Urine microalbumin/creatinine ratio annually; renal and hepatic function		Urine microalbumin/creatinine ratio annually
Treatment	Offer families of children with HbSS or Sβ^0 thalassemia information about hydroxyurea by 9 mo of age.[6,92–94]	Review available and future treatment options for SCD and adherence for patients on disease-modifying treatment.			
CNS screening	—	TCD ultrasonography screening annually for children with HbSS and Sβ^0-thalassemia from 2 to 16 y of age.[6] Repeat more frequently if the results are elevated			—
Eye screening	—	—	Begin screening for proliferative retinopathy with annual dilated fundoscopic examinations beginning at 10 y of age.		

TABLE 2 Continued

Psychosocial care	Provide information regarding support groups and other community-based organizations. Review Family Medical Leave Act with parent or caregiver.	Screen for developmental delay/cognitive impairment including academic/behavioral problems or symptoms of inattention, hyperactivity, or impulsivity. Consider neuroimaging and/or neurocognitive testing if present.		
		Discuss child care or preschool arrangements and resources to educate child care providers or school about SCD.	Provide families with educational materials about SCD to share with school personnel so a 504 plan and/or individualized education program can be developed. Review 504 plan/individualized education program annually. Discuss activities. Sports participation may induce painful episodes that may be prevented by increased hydration and taking breaks. Discuss educational and vocational goals. Encourage patient and family to seek assistance for mental health issues and provide guidance regarding appropriate providers if necessary.	Explain developing advanced directive, living will, and durable power of attorney. Address the need to keep insurance coverage active. Investigate whether patient should consider applying for disability insurance. Provide information regarding support groups and other community-based organizations to the patient. Explore personal beliefs about illness and existing sources of stress and support. Review Family Medical Leave Act with patient. Discuss academic and/or employment plans. Consider vocational opportunities. If appropriate, identify academic advisor and necessary accommodations.

CNS, central nervous system; TCD, transcranial Doppler. —, no screening recommendations.
[a] Amoxicillin may be used as an alternative, and erythromycin is appropriate for children with penicillin allergy. Routine use of antibiotic prophylaxis for infants with HbSC and $S\beta^+$-thalassemia is advised.[80,87,88]

and (3) gene editing to promote fetal hemoglobin induction. Current techniques require harvesting patient's own stem cells, modifying those cells in the laboratory, then eradicating patient's remaining bone marrow cells with chemotherapy followed by infusion of the genetically modified stem cells.[100] Although 2 commercialized approaches received US Food and Drug Administration approval in December 2023, the risks and long-term benefits of gene therapy still require investigation.

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.[6,8] Children with SCD with higher levels of parental support report less depressive symptoms and better quality of life, emphasizing this key component of care.[101] Personal and cultural beliefs about illness and existing stresses and support systems may greatly impact the ability to cope with SCD.[102] Extended family networks can provide an important support system for parents of children with SCD.[103] Patient support groups and community-based organizations can be important resources. Extended members of a dedicated sickle cell specialist team, such as nurse practitioners, physician assistants, nurse specialists, nurses, social workers, therapists, clinic navigators, and educational liaisons, can be vital in mentoring, supporting academic achievement, and ensuring that all patients receive information about best medical practices.[14] Relevant issues to discuss include health insurance coverage, transportation for health care, and education of peers and school personnel about SCD.[6–9]

GENETIC EDUCATION AND COUNSELING

The pediatrician or other pediatric primary care provider may be involved in the counseling of a patient or couple at risk for having a child with SCD. Education includes a review of autosomal recessive inheritance and the provision of accurate information about genetic risk and the clinical course of disease and trait, medical complications, and treatment of the specific SCD genotype relevant to the family.[16,20–22,26,68] 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 parental testing is essential. Such testing includes a CBC and hemoglobinopathy testing (as described previously). Solubility testing (such as SickleDex) is not adequate and is not recommended for carrier testing, because it will not identify individuals with hemoglobin C or β-thalassemia trait.

It is important that adolescents with SCD receive accurate information[16,20–22,26,68,104] about:

TABLE 3 Patient and Family Education

Education	Birth–12 mo	Years 1–4	Years 5–12	Years 13–17	Years 18–21
Genetics	Review the results of neonatal screening and confirmatory testing (Table 2) with parents or caregivers.	Review the results of hemoglobinopathy testing (Table 2) with parents or caregivers.		Discuss genetics, including partner testing, genetic counseling, and prenatal diagnosis with patient.	
Pathophysiology and patient knowledge	Discuss the basic pathophysiology and genetics of SCD, including the availability of carrier testing and prenatal diagnosis.	Review indications and risks for blood transfusions.			Review transfusion history and whether patient has alloantibodies.
		Discuss chronic manifestations of the disease, including proliferative retinopathy, cholelithiasis, avascular necrosis of the hip and shoulder, leg ulcers, and delayed growth and puberty.			—
		—	—	Discuss concerns and issues related to the impact of the disease in adolescence.	—
		—	—	Review laboratories values with patient. Patients should be knowledgeable about baseline laboratory values and type of SCD they have.	
Visit scheduling	Discuss the rationale and importance of periodic comprehensive evaluations.				
Medical home	Discuss medical home models (pediatric primary care provider versus comprehensive sickle cell program).			Patients should start scheduling their own appointments and requesting medication refills (with supervision).	Establish care with an adult primary care provider and sickle cell provider. This might be the same provider in less severely affected patients.
	Stress the need for coordinated care and communication among the family, pediatric primary care provider, and subspecialists. The roles and responsibilities of family and providers should be defined.				
	Reconsider the patient's medical home model depending on family preference and frequency and severity of complications.				
Prophylaxis, immunization, and prevention	Review the importance of penicillin prophylaxis (if appropriate), and immunizations, including pneumococcal and meningococcal vaccines.				
Fever management	Review the importance of urgent medical evaluation for and treatment of febrile illness (temperature ≥38–38.5°C).				
Acute complications	Discuss signs and symptoms of acute splenic sequestration and teach abdominal palpation for determining spleen size.	Review presentation and management of splenic sequestration and other anemic crisis, dactylitis, and other manifestations of pain and acute chest syndrome including when and where to seek care.	Review home management of painful events.	Review principles of pain management. Patients should be able to state pain triggers and appropriate treatment.	Review acute complications of disease (anemic crisis, fever, acute chest syndrome, etc) and management. Patients should understand when, where, and who to call/where to present for acute complications.
	Teach appropriate management of dactylitis and other painful events.		Reinforce anticipatory guidance regarding anemic crisis (including splenic sequestration for patients with HbSC and Sβ^+-thalassemia), acute chest syndrome, stroke, transient ischemic attack, and priapism, including when and where to seek care.		
	Discuss the significance of respiratory symptoms possibly indicative of acute chest syndrome.				

TABLE 3 Continued

Education	Birth–12 mo	Years 1–4	Years 5–12	Years 13–17	Years 18–21
CNS events	—	Discuss CNS manifestations of SCD and stress the importance of urgent evaluation for signs or symptoms suggestive of stroke or transient ischemic attack.			
Urogenital concerns		Discuss enuresis, which is common in children and adolescents with SCD related to hyposthenuria, sleep-disordered breathing, and a functionally small bladder.		Discuss sexuality and the availability of contraception options including levonorgestrel-releasing intrauterine device, depot medroxyprogesterone acetate implant, progestin-only oral contraceptive pills, etc.[105–107]	
		Discuss priapism, initial home management, and the need for urgent evaluation and treatment of recurrent or prolonged episodes (≥4 h).			
Activities	—	Discuss issues related to activity, including participation in athletics, avoidance of temperature extremes, and maintenance of hydration.			
Treatments	Review treatment options for SCD; if patient is on disease-modifying treatment, review adherence.				
	Review current medication list and how to request refills.			Review current medication list and reason for current medications. Over time, the patients should be able to do this independently. Patients should be encouraged to call for medication refills,	
	—	—		Medication effects on fertility and pregnancy should be reviewed.	
Transitioning	—	—	—	Review clinic transition policy. Discuss options for adult care primary care and subspecialty providers as well as insurance. Develop with the patient a plan for transition from pediatric to adult medical care.	Review medical summary with patient and provide copy for transition.
					If needed, have patient sign release of information to have medical records transferred to new providers.
Other	Provide written materials and/or reputable Web sites to reinforce education.	Determine whether a child has pica; pica is common and not related to iron status in SCD.	—	Discuss the importance of avoiding alcohol, tobacco, vaping, and street drugs, which may precipitate or exacerbate complications of SCD.	Discuss with patient methods of educating peers on basic information about SCD.

CNS, central nervous system. —, no screening recommendations.

- Genetic transmission of SCD—1 gene from each parent results in disease.
- Availability of carrier testing for partners—all offspring of a person with SCD will have at least 1 gene for SCD; the trait status of the partner will determine possibility of child with SCD.
- Prenatal diagnosis—availability of testing of fetus for SCD before birth (amniocentesis, chorionic villous sampling, or preimplantation genetic diagnosis), as well as assisted reproductive technologies including in vitro fertilization and preimplantation genetic diagnosis.
- Planning pregnancies—knowing the SCD or trait status of both partners.
- Contraception—levonorgestrel-releasing intrauterine device, depot medroxyprogesterone acetate injection, etonogestrel implant, and progestin-only oral contraceptive pills are preferred because of an increased risk of thrombosis in SCD, but for specific patients, combined low-dose estrogen or combined oral contraceptive pills, nonhormonal, or barrier methods may be preferred, particularly as backup contraception or for prevention of sexually transmitted infections. Method advised is unique to each patient circumstance and preference.[105–107]
- Effects of current medications on fertility and/or pregnancy.[108]

When an adolescent with SCD becomes pregnant, comanagement by a hematologist with expertise in SCD and a high-risk obstetrician is essential. Pregnancy is often associated with an increased frequency of SCD complications,[109] but most pregnancies in people with SCD have a successful outcome for the parent and infant.

TRANSITION

Transition from a pediatric to adult care model requires a structured but flexible process designed to address the intricacies of SCD. Historically, it has been a time of increased emergency department visits, hospitalizations, and mortality, likely because transfer rather than transition has occurred.[110,111] Successful transition requires self-efficacy and advocacy on the patient's part, as well as communication between the pediatric and adult primary care and specialty providers.[112,113] Insurance planning is critical, and discussions must begin in the mid-teen years. It also requires parental and community support, along with the identification of mental health and cognitive barriers.

Specific information about the transition of patients with SCD from pediatric to adult care can be found from various sources.[114,115] Special care must be taken to identify a site of both acute and ongoing care for college-bound students at home and at school, as well as a source of reproductive health care (specifically gynecology) from providers knowledgeable about SCD. There are many Internet-based resources to facilitate transition, including the Sickle Cell Transition E-learning Program (from St Jude Children's Research Hospital[116]), Got Transition from the Maternal and Child Health Bureau,[117] and Taking Charge of Your Health and Health Care plan from the CDC.[118] Generally, knowledge in medical, social, and employment/academic domains is an expectation for readiness to transition. The American Society of Hematology has a sickle cell transition readiness assessment tool and resources available online.[119]

HEALTH SUPERVISION FROM BIRTH TO EARLY ADULTHOOD

Improvements in care have resulted in almost all children with SCD surviving into adulthood and transitioning into adult care, which has allowed shifting the goal of care to improved quality of life. Optimal care does not occur in isolation but requires comanagement between the pediatric primary care provider and hematology specialist team. Psychosocial support is important throughout the age span, and availability of online resources is increasing. Tables 2 and 3 review the care of children with SCD from birth through transition (by age group), with an emphasis on health maintenance and education (patient and family), respectively.

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ABBREVIATIONS

CBC: complete blood cell count
CDC: Centers for Disease Control and Prevention
HbS: hemoglobin S
HbSC: sickle hemoglobin C disease
HbSS: sickle cell anemia
MRA: magnetic resonance angiography
NBS: newborn screening
PCV: pneumococcal conjugate vaccine
PCV15: 15-valent pneumococcal conjugate vaccine
PCV20: 20-valent pneumococcal conjugate vaccine
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
SCD: sickle cell disease

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

All clinical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

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