Accordant
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Clinical Practice Guidelines

Sickle Cell Disease

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INTRODUCTION

The AccordantCare™ program works with health plans to assess, monitor, and support those with certain complex, chronic conditions. The focus of the program is to improve health outcomes and prevent or limit disease-related complications. AccordantCare offers unique services at no additional charge to the patient, putting them in a strong position to adhere to their treatment plan.

There are several ways AccordantCare augments physicians' efforts. Through regular telephone contact, AccordantCare nurses:

- Keep patients informed about the disease process
- Coach patients in self-motivation and self-care skills
- Encourage patients to alert their physician when new symptoms arise
- Direct patients to resources that help pay for medication, transportation, home modifications, etc.
- Ensure preventive and screening measures are accomplished
- Provide emotional support to patients and caregivers
- Screen for depression
- Find local support groups

We invite physicians to make use of the services offered by AccordantCare and to suggest ways we can further patients' treatment goals. To offer feedback, get more information, ask questions, or voice concerns, call toll-free 1-800-948-2497 to speak with a program representative from 8 a.m. to 9 p.m., Monday through Thursday, and from 8 a.m. to 5 p.m. on Friday, Eastern Time. Messages left after hours will be returned the next business day.

Intent of Guidelines

The purpose of this Clinical Practice Guideline is to describe current patterns of practice where there is no fully established national guideline for diagnosis and management. It is not meant to dictate care of patients. Decisions about care are made by the physician and the patient based on the individual needs of that patient.

A patient's health plan may or may not pay for the all medicines, tests, equipment, or services mentioned in this document. Benefits should be checked with the individual's health plan to assure payment.

DISEASE OVERVIEW

Sickle cell disease (SCD) is a group of disorders in which a genetic mutation causes a single amino acid substitution on the beta chain of hemoglobin molecules, resulting in an abnormal hemoglobin.[1] These abnormal hemoglobin molecules tend to clump together and form long chains (polymers) after they release oxygen to the body's cells.

Red blood cells that contain abnormal hemoglobin often become bent and deformed from their usual biconcave shape. While most of these distorted red blood cells are irregularly shaped, some have a crescent or sickle shape. This sickle shape and other irregularities cause red blood cells to clog and be unable to move through small blood vessels. When the sickled blood cannot reach microscopic regions of tissue, the result is low tissue oxygen, pain, and tissue and organ damage.

The primary signs and symptoms of SCD include anemia, repeated infections, and periodic episodes of pain and tissue injury. These signs and symptoms usually begin in early childhood, vary in severity from person to person, and can affect almost every part of the body.[1]

Classifications of Sickle Cell Disease

The four most common variants of SCD, in order of frequency in the United States population, are[2]:

1. sickle cell disease-SS;
2. sickle cell disease-SC;
3. sickle cell disease-Sβ^+ thalassemia; and
4. sickle cell disease-Sβ^0 thalassemia.

Accordant manages patients with any type of SCD. Regardless of the genotype, many of the complications of SCD can range from mild to life-threatening in any one individual.[2]

Prevalence/Incidence

Sickle cell disease affects millions of people worldwide. In the United States, sickle cell disease is the most common inherited blood disorder, affecting 80,000 to 100,000[1,3] people. About 50,000 people in the United States have the most severe form of SCD, sickle cell anemia.[4]

The incidence of SCD in the United States exceeds that of most other serious genetic disorders including cystic fibrosis and hemophilia.

Financial Considerations[5]

The estimated cost of SCD care in the US exceeds $1.1 billion. About 80% of costs are associated with hospitalizations. Interventions that reduce

complications such as acute pain episodes may result in significant cost savings. The cost of SCD varies significantly across age groups, with older patients utilizing more of the resources.

DIAGNOSIS OF DISEASE

Newborn screening

- Hb isoelectric focusing[6]
- High performance liquid chromatography (HPLC) fractionation[6]

DNA gel electrophoresis [7]
HbS solubility test (screening test) (> 6 months of age)[6]

APPROACH TO MANAGEMENT OF PRIMARY CONDITION

For the best results, healthcare for children with SCD requires professionals with expertise in the management and treatment of SCD, including a pediatric hematologist working in conjunction with a multidisciplinary team. In addition to treatment with medicines as needed, the comprehensive care of patients with SCD includes

- genetic counseling,
- ongoing patient and family education,
- periodic health evaluations, and
- appropriate preventive measures.[8]

Preventive Measures

Immunizations—Children with SCD should receive all the immunizations recommended by the American Academy of Pediatrics and the Centers for Disease Control and Prevention (CDC), including vaccination against hepatitis B and the annual flu vaccine (beginning at 6 months of age and older).[9] In addition, there are specific considerations for children with SCD.

Adults with SCD should also receive all vaccinations according to CDC recommendations.

Prophylactic penicillin—The most important intervention in the routine treatment of children with SCD is penicillin to prevent pneumococcal infection.[10] Treatment with penicillin should begin by two months of age.[2] Children with SCD who do not have a history of invasive pneumococcal infection or who have not had their spleen removed can stop taking preventive penicillin at age five.[8,10] For those with documented, recurrent *S. pneumoniae* infections, preventive penicillin may be continued at least through 7 years of age and up to age 10.[11]

Medications to Treat Sickle Cell Disease

Hydroxyurea (HU)—has been shown to reduce mortality in adults,[12] but it is probably underutilized. A 2013 study found that increased use of HU was associated with decreased hospitalization rates and reduced frequency of blood transfusions for these SCD patients outside of a clinical trial setting.[13] It is FDA

approved to reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises (generally at least 3 during the preceding 12 months).[14]

Although hydroxyurea is not yet approved by the FDA for use in very young children, the results of the Pediatric Hydroxyurea Phase III Clinical Trial (aka BABY HUG)[15] have led the National Heart, Lung, and Blood Institute to encourage healthcare professionals to consider use of hydroxyurea in children who have sickle cell disease as early as possible.[16] Strong evidence shows that hydroxyurea reduces hospitalization and increases total hemoglobin and HbF in children with severe HbSS.[17]

Pervasive concerns exist about the safety of HU for children, even among parents of current users. These include concerns about the unknown carcinogenic potential and other adverse effects of HU. Survey data underscore the need for strategies to bolster parental understanding about the benefits of HU and to address concerns about its safety.[18]

Recommended Nondrug Therapies

Transfusions[10]—Doctors use transfusions for sickle cell patients to decrease the proportion of sickle red cells and to raise the oxygen-carrying capacity of blood. Episodic, acute transfusions are used to stabilize or reverse severe SCD complications. Evidence suggests that patients with SCD should be offered transfusions before low- or medium-risk surgeries to lower the risk of serious adverse events.[19] Recurring, long-term transfusions are used to prevent future complications.

Present data support the safety and potential benefits of involvement of SCD patients in physical activities, provided that the intensity is not excessive. Regular exercise at moderate intensity could decrease the risk of inflammatory reaction related to exercise and could increase the patient's vasodilatory reserve, which in turn may decrease the risks for vaso-occlusive crisis.[20]

PREVENTION AND MANAGEMENT OF COMPLICATIONS

Accordant helps patients prevent and manage complications by teaching early warning signs, encouraging adherence to treatment plans, offering supportive care, and recommending physician contact where needed. The goals and cooperative interventions below do not represent a comprehensive list of complications but reflects some of the more common clinical situations specific to sickle cell disease. General health topics (e.g., age-appropriate cancer screening) are beyond the scope of this document.

Goal: Improve self-management skills

Cooperative interventions include teaching patients/parents the importance of:

- personal motivation building;
- development of prevention-focused, self-management skills;
- confidence and communication;
- adhering to treatment plan;
- knowledge development; and
- planning for the transition of care from the parent/caregiver to the adolescent.[21,22]

Goal: Facilitate early detection and treatment of acute chest syndrome
Cooperative interventions include teaching patients/parents to:

- recognize the symptoms (e.g., chest pain, fever, cough) of acute chest pain syndrome[2];
- understand the importance of seeking prompt medical attention for acute chest syndrome;
- understand the treatment options, including transfusion or hydroxyurea therapy; understand that moderate evidence suggests that early use of HU can reduce the incidence of acute chest syndrome in patients with low hemoglobin levels[23]; and
- consider the use of incentive spirometry for children with SCD admitted to the hospital for nonpulmonary complaints.[24]

Goal: Prevent or manage pain and acute pain episodes
Cooperative interventions include teaching patients/parents to:

- understand that effective pain management in children with SCD requires multidimensional, comprehensive approaches that target three factors:
  - psychological (e.g., coping, pain tolerance, and control);
  - social (e.g., parent responses to pain, home management techniques); and
  - physiological (e.g., inflammation, tissue ischemia)[25];
- understand the importance of treating <u>mild pain</u> to avoid the progression to more severe pain:
  - manage with acetaminophen, NSAIDs (in the absence of abnormal renal function);
  - manage uncomplicated pain episodes at home with oral fluids, oral pain relievers, and coping/comfort measures—for example, heat or ice packs, massage, menthol cream rubs, increased fluid intake, distraction, guided imagery,[26] prayer, self-hypnosis, and relaxation techniques[2];
- see a doctor right away if they experience any <u>complicated pain event</u> involving:
  - the abdomen, especially with increasing jaundice or vomiting[2];
  - chest pain[2] or respiratory symptoms[10];
  - severe headache or other neurologic symptoms[2] such as partial or complete paralysis[10];
  - acute joint swelling[10];

  - prolonged, painful erection[10]; and
  - fever[2]

- understand that use of hydroxyurea has been shown to decrease the number of acute pain episodes in adults[12,27] and children[17];
- understand the importance of drinking lots of fluids;
- avoid conditions that might trigger a painful episode, including
  - overexertion,[2] especially if they have an enlarged spleen[28]
  - becoming dehydrated
  - stress
  - exposure to cold temperatures[2] (e.g., swimming in cold water)
  - infections
  - decongestants such as pseudoephedrine[29]
  - travel in an unpressurized aircraft
  - high-altitude places[28]
  - smoking and second-hand smoke[28]
  - consuming alcohol
- work with their Accordant nurse and doctors to develop an individualized pain management plan that summarizes the pertinent aspects of patient data. In some situations, the treatment plan may be transformed into an ID card to be carried by the patient and presented to a care provider as needed.[30]

Goal: Minimize impact/decrease incidence of aplastic crisis
Cooperative interventions include teaching patients/parents to:

- recognize the symptoms of an aplastic crisis and report them to their doctor:
  - preceded by or associated with fever[10]
  - pallor[2]
  - fatigue[2]
  - headache[10]
  - difficulty breathing[10]
  - severe anemia[10];
- understand that human parvovirus B19 infection (fifth disease) can lead to aplastic crisis;
- recognize the symptoms of human parvovirus B19 infection and relay those symptoms to their doctor[31]:
  - fever
  - abdominal pain
  - musculoskeletal pain
  - nausea/vomiting
  - malaise
  - headache
  - runny nose
  - rash[31]

- avoid people or environments infected with human parvovirus B19, especially during late winter and early spring months; and
- use frequent hand washing as a practical, effective method to decrease the chance of becoming infected human parvovirus B19.

Goal: Minimize the impact of bone issues.
Cooperative interventions include teaching patients/parents to:

- recognize the symptoms of:
  - bone marrow expansion (long arms and legs, misshapen skull, protrusion of the incisors and overbite[10], compression fractures of vertebrae and rounded upper back[10]),
  - occlusion of blood vessels in the bone[10] (local tenderness, pain, warmth, and swelling, impaired motion of nearby joints, dactylitis or hand-foot syndrome in children, fever—absent or low-grade), and
  - bone infection[10] (local tenderness, warmth, and swelling; high fever with infection; severe pain and marked limitation of motion for septic arthritis);
- seek prompt medical attention if they experience any of the signs and symptoms of bone problems;
- consider hydroxyurea or chronic transfusions for prevention of further problems and;
- understand their treatment options (e.g., pain management, surgery, antibiotics) for bone problems.

Goal: Control/prevent vitreous bleeding and retinal detachment.
Cooperative interventions include teaching patients/parents to:

- understand the importance of having annual eye exams beginning in childhood and continuing through adulthood;
- recognize the seriousness of vision changes; and
- seek prompt medical attention for any eye problems they experience.

Goal: Recognize gallbladder disease early and seek appropriate treatment.
Cooperative interventions include teaching patients/parents to:

- understand the symptoms of gallbladder problems (e.g., abdominal or back pain after meals, jaundice, nausea/vomiting)[2];
- report symptoms they experience to their doctor as soon as possible;
- eat a healthy diet with limited fried and fatty foods.

Goal: Facilitate early diagnosis and treatment of heart problems.
Cooperative interventions include teaching patients/parents to:

- understand the symptoms of SCD-related heart problems (e.g., chest pain)[10];
- report any symptoms of SCD-related heart problems they have to their doctor as soon as possible; and

- understand the treatment options for heart problems, which may include increasing hemoglobin in severely anemic patients with transfusion or hydroxyurea therapy.[10]

Goal: Prevent or achieve early recognition and prompt treatment of infections.
Cooperative interventions include teaching parents to:

- seek prompt medical attention for their children with SCD who run a fever, defined as 100.4°F or higher for children younger than six months, and 101.3°F or higher for children six months or older[2];
- understand the importance of vaccinations and preventive penicillin;
- practice good hygiene and make sure that children wash their hands frequently[29];
- know the early symptoms of infection and when to seek medical help;
- work with their children to focus on preventive dental health care and on the early identification and treatment of dental infections[32]; and
- share information about a child's needs with teachers and other caretakers as appropriate.[28]

Goal: Recognize iron overload early to prevent end organ damage and to minimize the side effects of chelation therapy with deferoxamine or deferasirox.
Cooperative interventions include teaching patients/parents to:

- avoid excess dietary iron;
- understand the need for regular monitoring for iron overload (see Patient Follow Up section); and
- understand the importance of adhering to chelation therapy.

Goal: Minimize the impact of leg ulcers
Cooperative interventions include teaching patients/parents to:

- understand the importance of recognizing and reporting ulcers early so treatment can begin;
- understand that treatment of leg ulcers requires patience and time;
- understand the basics of wound care, including when and how to change their dressing.[10]

Goal: Control/minimize the impact of liver disease.
Cooperative interventions include teaching patients/parents to:

- understand that hepatitis C may have no symptoms or that symptoms may be mild (e.g., fatigue, abdominal pain);
- understand that treatment usually involves interferon therapy but there is no consensus for treatment of hepatitis C in patients with SCD;
- understand the symptoms of cholestasis (e.g., jaundice, dark urine, pale-colored stools) and the need to report them to a doctor; and
- understand red cell transfusion is a possible treatment option for cholestasis.

Goal: Facilitate early detection and minimize impact from pulmonary hypertension.
Cooperative interventions include teaching patients/parents to:

- understand that pulmonary hypertension is a significant cause of morbidity and mortality in sickle cell patients,[33] especially in those with SCD-SS or SCD-β^0 thalassemia;
- know that children can be affected, especially in those with high hemolysis and/or low hemoglobin[34,35];
- be aware that pulmonary hypertension may be asymptomatic but that if symptoms do exist, they usually involve difficulty breathing, either unexplained or upon exertion;
- understand the importance of talking to their doctor about early detection via transthoracic Doppler echocardiography[35-37];
- know that most of the recommendations for managing SCD-related pulmonary hypertension are based on expert opinion or extrapolated from data derived from managing other forms of pulmonary hypertension[36];
- understand that the treatment options may include maximizing hydroxyurea therapy or the use of vasodilator or antiremodeling agents.[36]

Goal: Prevent stroke
Cooperative interventions include teaching patients/parents to:

- understand the types of stroke and the signs and symptoms of each type and report any symptoms they experience to a doctor as soon as possible;
- understand that children who have had one clotting stroke have a 60% to 90% chance of having another stroke[2];
- understand the importance of early recognition and treatment for people at high risk for stroke, including those with
    - high blood flow velocity on transcranial Doppler (TCD)[38]
    - HbSS genotype
    - low hemoglobin levels[38]
    - low HbF levels
    - high white blood cell count[38]
    - relative high blood pressure (i.e., higher than the lower-than-normal blood pressures associated with SCD)
    - previous silent stroke[38]
    - history of TIA[39]
    - history of acute chest episodes[38]
    - nighttime low blood oxygen
    - migraine headaches[40]
    - severe anemia[39]
- discuss with their doctor transcranial Doppler screening as an important measure of stroke risk and prevention;
- know that children 2 to 16 years with SCD-SS or SCD-Sβ^0 thalassemia are most at risk and should be tested with TCD[10] and that it is reasonable to repeat a TCD annually[38];

- understand the importance of regular transfusions[41] or hydroxyurea therapy in preventing strokes, and that moderate evidence suggests that early use of HU can reduce the incidence of increased TCD velocities and stroke in patients with low hemoglobin levels[23];
- understand the adverse side effects of their treatment and report any they experience to their doctor;
- find sources of outpatient rehabilitation and support;
- understand that all patients experiencing a TIA should receive the appropriate therapy for stroke prevention[42]:
    - Adults with previous TIA may consider antiplatelet agents (e.g., aspirin) and should make every effort to gain control over traditional modifiable risk factors like blood pressure, cholesterol, and glucose levels.
    - Adults and children with a previous ischemic event may be considered for regular transfusion therapy (HbS <30% to 50% of total hemoglobin), hydroxyurea, or bypass surgery of cerebral blood vessels (advanced occlusive disease).

Goal: Decrease occurrences of priapism and prevent impotence.
Cooperative interventions include teaching patients/parents to:

- discuss priapism openly and honestly;
- know that priapism is very serious and can lead to impotence in the future;
- learn the signs and symptoms of priapism and report any they experience to their doctor;
- seek emergency medical help if an episode of priapism lasts more than two hours[10];
- avoid a full bladder or prolonged sexual activity, both of which can trigger priapism[10];
- drink extra fluids and to try to urinate as soon as possible if they are already experiencing an episode of priapism[10];
- never use ice or cold packs on the penis;
- use recommended oral analgesics for the pain[10];
- know that diethylstilbestrol and hydroxyurea have been tried for prevention[43];
- understand treatment options (e.g., transfusion[10], aspiration[10], medication [terbutaline and phenylephrine]).

Goal: Help children achieve a positive self-image and as normal a quality of life as possible.
Cooperative interventions include teaching parents to:

- emphasize the child's strengths and talents and provide positive reinforcement for all accomplishments[44];
- discourage children with SCD from blaming anyone for their disease and for their limitations[44];

- be aware of the possibility of slow growth and delayed puberty in adolescents with SCD, and help children with their concerns about any failure to thrive;
- assist school-age children in maintaining a school schedule by educating teachers, school nurses, and other school staff about sickle cell disease;
- facilitate continuity when children are home sick or hospitalized by requesting that teachers assign a study partner to bring notes and assignments to the child;
- find special activities and a sickle cell camp for children as a way of encouraging independence and communication with others who have sickle cell disease;
- seek out support groups, especially for early adolescents[45]; and
- participate in vocational rehabilitation and job training programs.

Goal: Recognize the symptoms of acute splenic trapping early and minimize impact.
Cooperative interventions include teaching patients/parents to:

- Recognize that acute splenic trapping may be asymptomatic[2] or cause one or more of the following symptoms:
  - sudden weakness[10]
  - pallor[2]
  - rapid heart rate and breathing[10]
  - abdominal fullness[10]
  - lethargy[2]
  - upper left quadrant tenderness[2]
  - enlarged spleen[2];
- understand that an attack can lead to significant morbidity and remains a leading cause of death in children with SCD[10];
- take the appropriate action to obtain rapid evaluation and treatment;
- know that this complication is frequently associated with viral and bacterial infections[10];
- understand the treatment options:
  - For patients who have a life-threatening episode of acute splenic trapping that requires transfusion support, the spleen may be removed shortly after the event or they should be placed on a chronic transfusion program.[10]
  - For very young infants who suffer a severe episode, chronic transfusions can keep the patient's HbS levels below 30% until they reach two years of age, when their spleen may be removed[10,40];
- ask the doctor how to[2,10]
  - palpate the spleen and measure its size;
  - make and use a "spleen stick." [46]

Goal: Encourage pregnancy planning and help assure the best possible outcomes for mother and baby.

Cooperative interventions include teaching patients/parents to:

- understand the genetics of SCD and the probability of having a child with SCD;
- know that women who are pregnant should not take hydroxyurea because of its teratogenic effects. Pregnancy should be avoided while a woman or her male partner is taking hydroxyurea;
- know and understand the potential complications of pregnancy for both the mother and fetus;
- understand the importance of maintaining good health habits during pregnancy, including taking the usual vitamin, mineral, and folate supplements; and
- understand the options for treatment during pregnancy and after delivery.

PATIENT FOLLOW-UP[47]

Monitor:

- History and physical exam every 6 to 12 months
- Degree of anemia: CBC, differential, and reticulocyte count every three to four months
- Iron overload (in patients with chronic transfusions): serum ferritin every 2-3 months[48]
- Potential end-organ complications: every 6 to 12 months if indicated:
    - biochemical profile
    - LFTs, hepatitis serology
    - urinalysis with microscopy
    - microalbumin
    - urine culture
    - chest X-ray
    - ECG
    - arterial blood gases
    - pulse oximetry
    - echocardiography
    - transcranial Doppler (TCD)
    - pulmonary function tests (PFTs)
    - annual hearing and eye evaluations if on chronic iron chelation
    - X-ray or MRI of joints
- Hydroxyurea side effects: hematologic and biochemical profiles and HbF level at baseline, every month after treatment initially or after increasing the dose, and every 1 to 2 months after dose is established; in children, monitor until a stable maximum tolerated dose is established using:
    - reinforcement of daily adherence (monthly);
    - a physical examination focused on potential toxicities (monthly);

  - complete blood count with WBC differential and reticulocyte count (monthly); and
  - liver and kidney function tests as well as a hemoglobin electrophoresis (every 3 to 6 months).[17]

- Avascular necrosis: consult orthopedic specialist as needed
- Retinopathy: annual eye exam[10]
- Quality of life, dependence on pain medicine as needed
- Use of alternatives for pain control such as yoga, acupuncture, relaxation training, biofeedback, massage therapy, mindful meditation, etc.
- Pain relief, infections, organ failure, iron chelation: adjust doses of analgesics, adjuvant, hydroxyurea, folic acid, antibiotics, deferoxamine as needed

PATIENT EDUCATION

The Sickle Cell Information Center http://scinfo.org/

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