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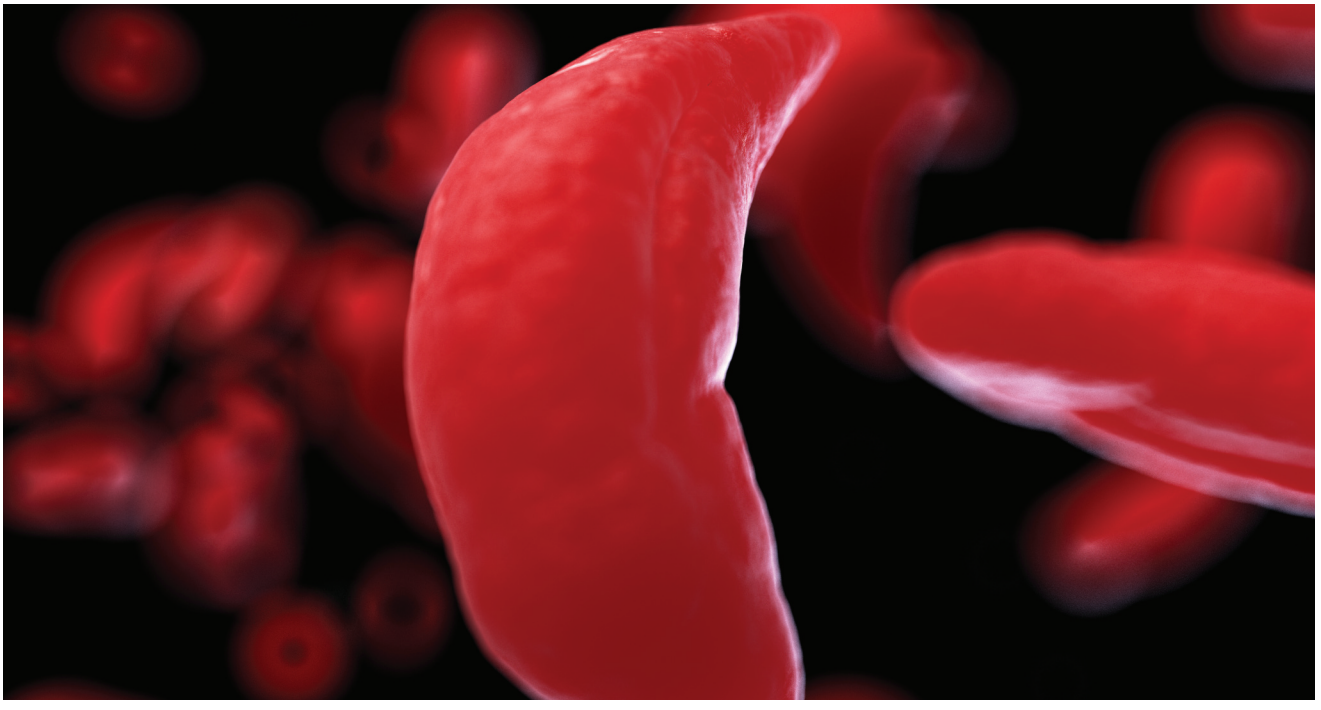

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Managing patients with sickle cell disease in primary care

Robert J. Hehre, MPAS, PA-C, RCO

ABSTRACT

Sickle cell disease (SCD) is a group of disorders affecting the hemoglobin in erythrocytes. SCD is associated with significant morbidity and mortality and occurs most commonly among people of African ancestry. In 2014, the National Heart, Lung, and Blood Institute updated its guidelines for the management of SCD. These guidelines were implemented to provide evidence-based recommendations to assist primary care clinicians in the proper management of patients with SCD. This article reviews the current practice guidelines for SCD, with attention to health maintenance and hydroxyurea.

Keywords: sickle cell disease, anemia, erythrocytes, blood disorder, health maintenance, hydroxyurea

Learning objectives

- Review the epidemiology, cause, pathogenesis, clinical manifestations, and complications of SCD.
- Outline the current NHLBI health maintenance recommendations.
- Review the disease-modifying therapies available for SCD, with attention to hydroxyurea.

Sickle cell disease (SCD) is a group of inherited blood disorders affecting the hemoglobin molecules. Under deoxygenated conditions, erythrocytes become rigid crescents because of the defective hemoglobin. These sickle-shaped red blood cells are responsible for the chronic anemia, vaso-occlusion, hemolysis, and end-organ damage seen in patients with SCD. SCD affects thousands of people in the US and millions worldwide.[1] In 2014, the National Heart, Lung, and Blood Institute (NHLBI) released updated guidelines on the management of SCD, including assisting healthcare providers in offering routine SCD-related health maintenance, recognizing and treating SCD-related complications, and providing the indications for and monitoring of hydroxyurea and blood transfusion therapy.[2] Although the target audience of these guidelines

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Key points

- SCD is a chronic disorder with high morbidity and mortality.
- Despite the availability of the 2014 NHLBI guidelines for SCD management, primary care providers may not be aware of or familiar with them.
- Health maintenance recommendations for patients with SCD can be performed in a primary care setting.
- Education on hydroxyurea, as well as continued monitoring, can be done in a primary care setting.

are "primary care providers and other clinicians, nurses, and staff who provide emergency or continuity care to individuals with SCD," many primary care providers (PCPs) may be unfamiliar with them.[2,3] This article reviews SCD and optimal primary care management of patients with SCD, with a focus on hydroxyurea, which can be monitored routinely in a hematology or a primary care setting.

EPIDEMIOLOGY

SCD affects millions of people throughout the world.[1] The highest prevalence is found throughout most of the African continent, the Middle East, and India because of the protection that the sickle cell gene provides against malaria.[4] Due to population migration, SCD can now be found throughout the world. According to the CDC, about 100,000 patients in the United States have SCD, with the highest prevalence in Black patients.[1] SCD occurs in 1 out of every 365 Black births and 1 out of every 16,300 Hispanic births in the United States.[1] Additionally, 1 in 13 Black infants are born with sickle cell trait.[1] The number of newborns born with sickle cell anemia worldwide will likely increase from about 300,000 in 2010 to more than 400,000 by 2050.[5]

CAUSES OF SCD

SCD is an inherited disorder caused by a beta-hemoglobin gene mutation, leading to coding of the amino acid valine instead of glutamate in position 6 on the beta-globin chains.[6] This single amino acid substitution changes the molecular properties of the normal adult hemoglobin (HbA) to that of the mutant sickle hemoglobin molecule, denoted as hemoglobin S (HbS).[6] Depending on the type of SCD, either all or some of the HbA is replaced by HbS, causing various degrees of severity. The most common type of SCD is the autosomal recessive homozygote HBSS.[6] Other SCD types include combinations of HbS and other inherited blood disorders, such as HbSC, HbS-beta$^+$-thalassemia (beta$^+$ meaning some HbA production), and HbS-beta^0-thalassemia (beta^0 meaning no HbA production). HbSS and HbS-beta^0-thalassemia are clinically indistinguishable because the Hb beta^0 gene produces no functioning adult hemoglobin. These two genotypes are commonly referred to as sickle cell anemia (SCA) and are also the most severe forms clinically.[6] Sickle cell trait is not considered a type of SCD because clinical manifestations are rare and patients with this type generally do not experience symptoms.[2]

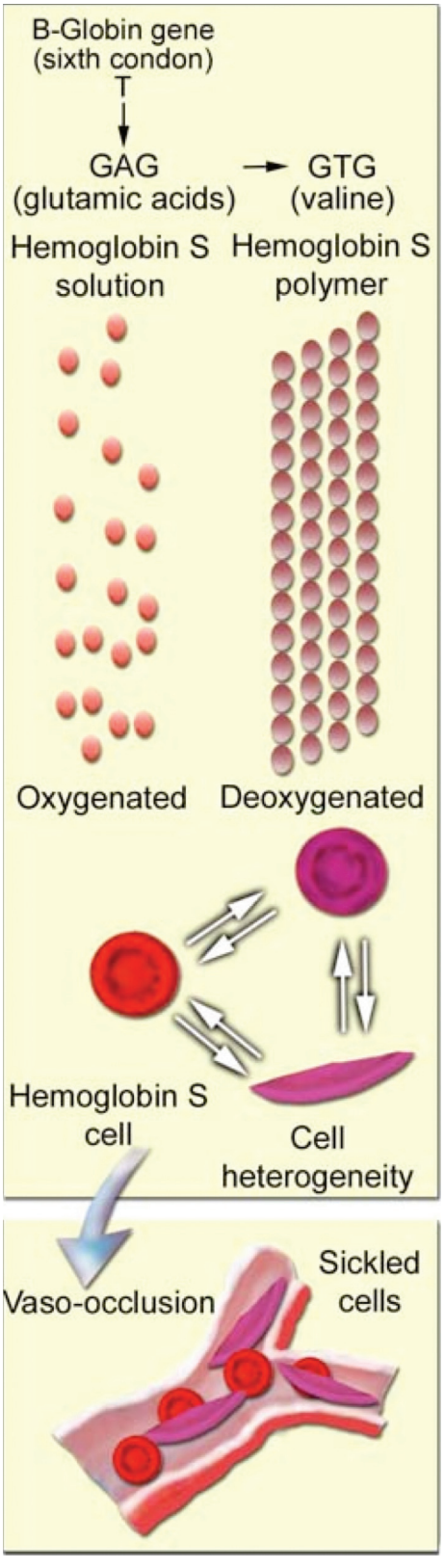
PATHOGENESIS

Under deoxygenated conditions, HbS molecules have the propensity to adhere to each other, forming long polymers within the erythrocyte (**Figure 1**).[6,7] Continued HbS polymerization eventually involves the membrane of the erythrocyte, leading to an imbalance and destruction of membrane ion channels, membrane rigidity, and morphing of the erythrocyte membrane into the characteristic sickle shape (**Figure 2**).[6] The propensity for HbS to polymerize is concentration-dependent, meaning that the likelihood of HbS polymerization in the erythrocyte is directly proportional to the concentration of HbS in the erythrocyte.[7] The rigidity of sickled erythrocytes also makes them more difficult to pass through smaller vessels, increasing the chances of occlusion. Moreover, abnormal erythrocyte membranes become damaged and fragile, causing them to lose water and cations, leading to hemolysis.[7,8] The specific pathogenesis of SCD-induced vaso-occlusion, however, is multifactorial, and involves more than just sickled erythrocytes clogging small blood vessels. The sickling event triggers a cascade of interactions involving the intravascular endothelium and surrounding cells. Sickled erythrocytes interact with the vascular endothelium more than unaffected erythrocytes through increased expression of membrane receptors, causing them to be more adhesive.[7,8] Baseline leukocyte, reticulocyte, and platelet counts tend to be higher in patients with SCD.[9] The leukocytes and reticulocytes present in patients with SCD also are more adhesive to the epithelium than in patients without SCD.[8,10] Nitric oxide expression, which is important in local vasodilation, is decreased in patients with SCD. Proposed mechanisms for decreased nitric oxide expression include endothelial dysfunction as well as the increase in free hemoglobin (a nitric oxide scavenger) from chronic hemolysis.[11,12] Collectively, these mechanisms cause cell adhesion, inflammation, and vaso-occlusion in the microcirculation, resulting in tissue ischemia and damage, chronic hemolysis, and end-organ damage.

CLINICAL MANIFESTATIONS AND COMPLICATIONS

The clinical complications of vaso-occlusive episodes in patients with SCD can affect nearly every organ system of the body (**Table 1**). Symptoms generally begin to manifest as early as age 6 months, as fetal hemoglobin (HbF) decreases and HbS increases to concentrations necessary for polymerization.[6,7] The earliest recognizable symptoms in infants usually include dactylitis, the characteristic swelling of the digits from vaso-occlusion.[13] However, potentially life-threatening complications such as acute chest syndrome (ACS) or severe septicemia from

FIGURE 1. Molecular and cellular changes of hemoglobin S



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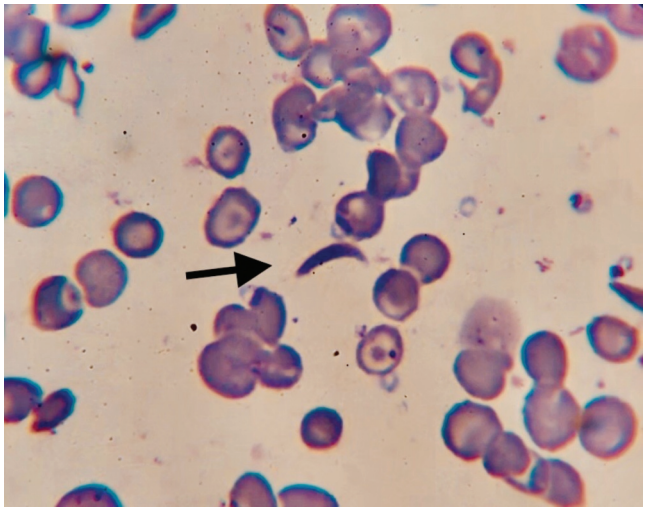
splenic dysfunction may be the initial presenting symptoms.[13] During childhood and early adolescence, physical growth and sexual development are commonly delayed. Patients with SCD usually are thin with relatively low body fat.[13]

Vaso-occlusive episodes continue throughout the patient's life. A vaso-occlusive episode (previously known as a vaso-occlusive crisis) is defined as pain resulting from tissue ischemia caused by vaso-occlusion.[2] The pain usually is acute, severe, and can manifest in nearly every part of the body, including the digits, bones, abdomen, head, and chest.[2] Acute and chronic complications also can arise from vaso-occlusive episodes. Some of these include acute anemia, acute kidney injury, acute chest syndrome, acute ocular damage, stroke, priapism, hepatobiliary complications, and bacterial infections secondary to splenic dysfunction.[2,6] **Table 2** contains measurable parameters of some SCD-related complications that may be unfamiliar to PCPs. A comprehensive list of SCD-related complications and their management is beyond the scope of this article. Further details on the diagnosis and management of acute and chronic complications can be found in the NHLBI guidelines.[2]

Chronic and repeated sickling events eventually lead to end-organ damage. Examples include chronic hemolytic anemia, splenic dysfunction (typically present as early as age 1 to 2 years), renal disease, and pulmonary hypertension.[6,7] Acute and chronic organ dysfunction from repeated sickling events lead to early mortality.[6]

Studies have shown that increased mortality has been linked to the number of vaso-occlusive episodes experienced by a patient.[14] However, the damage caused by SCD is not always clinically evident. The abnormal erythrocytes continuously circulate, causing micro-occlusion and poor tissue perfusion. This leads to years of continuous damage

FIGURE 2. Sickled erythrocyte seen under a microscope, using Giemsa staining



to tissue and organs, even in the absence of overt and obvious clinical manifestations.[6] PCPs should be vigilant in recognizing complications, which can be life-threatening and/or cause permanent damage.

HEALTH MAINTENANCE

To help prevent or delay SCD-related complications, the NHLBI has composed a set of health maintenance recommendations that can aid in the early recognition of end-organ damage and can reduce susceptibility to infections secondary to splenic dysfunction (**Table 3**).[2] PCPs can order recommended imaging and laboratory tests, refer patients to the appropriate specialists, and ensure that patients are up-to-date on vaccinations and adherent to prophylactic antibiotics.

TABLE 1. SCD-related complications[2]

Systemic
- Septicemia
- Multisystem organ failure

Circulatory system
- Left ventricular diastolic dysfunction
- Ventricular hypertrophy
- Aplastic crisis
- Acute anemia

Respiratory system
- ACS
- Pulmonary hypertension
- Restrictive and obstructive lung disease

Nervous system
- Meningitis
- Stroke
- Chronic neuropathic pain
- Proliferative sickle retinopathy
- Central retinal artery occlusion
- Orbital infarction
- Vitreous hemorrhage

Gastrointestinal system
- Acute hepatic sequestration
- Cholelithiasis and choledocholithiasis
- Acute cholecystitis
- Biliary sludge
- Acute intrahepatic cholestasis (sickle cell hepatopathy)

Genitourinary system
- Sickle cell nephropathy
- Acute renal failure
- Papillary necrosis
- Hyposthenuria
- Chronic kidney disease
- Priapism

Musculoskeletal system
- Osteomyelitis
- Avascular necrosis

Reticuloendothelial system
- Defective or absent splenic function
- Splenic sequestration

Integumentary system
- Leg ulcers

HYDROXYUREA

Therapies are available that can decrease the frequency of vaso-occlusive episodes and SCD-related complications rather than just acutely managing symptoms once they present. Hydroxyurea is a once-daily oral medication that is comparably inexpensive, easy to take, and has been extensively studied. It is an antineoplastic and myelosuppressive agent also used to treat a wide range of disorders, such as chronic myelogenous leukemia, solid tumors, psoriasis, polycythemia vera, and HIV.[6,11] In 1998, hydroxyurea was approved by the FDA for the treatment of SCD in adults.[2]

The drug is recommended for adults with any acute or chronic pain that regularly interferes with their quality of life. Examples include three or more vaso-occlusive episodes in 1 year, history of severe and/or recurrent acute chest syndrome, or symptomatic chronic anemia.

Following further seminal studies demonstrating the safety and efficacy in children, the NHLBI now includes recommendations for hydroxyurea use in adolescents, children, and infants.[2] Despite its known benefits and off-label use in infants and children, hydroxyurea was not FDA-approved for the treatment of SCD in children until December 2017.[15] The NHLBI recommends that hydroxyurea be offered to infants age 9 months and older, children, and adolescents regardless of clinical severity.[2]

Despite its recognition as a primary treatment for SCD, hydroxyurea is still being underused. Recognized barriers include the limited number of physicians with knowledge and experience using hydroxyurea, and patients' misconceptions and fears about adverse reactions.[2,16] Hydroxyurea also requires close and continued monitoring, including frequent healthcare provider appointments, ranging from every 4 weeks early in treatment to every 3 to 6 months long-term. These appointments are necessary to review patient adherence, screen for adverse reactions, and to draw the appropriate laboratory samples for monitoring the effectiveness and toxicities of hydroxyurea.[2,11,16] However, the American Society of Hematology recognizes the role primary care can play by stating that monitoring can be conducted routinely in a hematology or a primary care setting.[16] With an understanding of hydroxyurea, PCPs could assist in providing patient education, encouraging adherence, alleviating misconceptions concerning adverse reactions, and helping to monitor its use.

Mechanism of action How hydroxyurea prevents vaso-occlusive episodes in patients with SCD is not completely

understood. However, several mechanisms have been recognized. The most important mechanism is inhibition of ribonucleotide reductase, an enzyme necessary for DNA synthesis. By inhibiting ribonucleotide reductase, hydroxyurea causes a temporary arrest in hematopoiesis, which triggers a stress erythropoiesis in the bone marrow. Consequently, the marrow begins to produce erythrocytes from earlier erythroid progenitors that still maintain their HbF-producing capacity, resulting in an increase in HbF production and decrease in HbS production.[11] HbF lacks the ability to adhere to other hemoglobin molecules and interrupts HbS polymerization and erythrocyte sickling.[17] Greatest results have been shown when the HbF percentage has doubled from baseline or has increased more than 20%.[15,18]

Hydroxyurea also reduces production of leukocytes, reticulocytes, and platelets; reduces leukocyte, reticulocyte, and erythrocyte expression of surface adhesion receptors; improves erythrocyte rheology including elevated mean corpuscular volume (macrocytosis); increases nitric oxide production; and reduces nitric oxide consumption.[11,19,20] The synergistic combination of these mechanisms enables hydroxyurea to combat both the obvious and overt pathophysiologic effects of SCD.

Initiation and titration Hydroxyurea is usually initiated by a hematology specialist at 15 mg/kg/day in adults and 20 mg/kg/day in children, with lower doses if the patient has reduced renal function.[2] During the dose escalation phase, the daily dose is increased by 5 mg/kg/day every 8 weeks, or sooner if a painful vaso-occlusive episode occurs. The maximum dose is 35 mg/kg/day.[2] To get the most clinical benefit, dose escalation continues until there is mild myelosuppression (absolute neutrophil count between 2,000/mcL and 4,000/mcL); the dosage at this point is considered the maximum tolerated dose.[2] Toxic blood counts in a patient on hydroxyurea are an absolute neutrophil count less than 2,000 cells/mcL (or 1,250 in younger patients with lower baseline counts), platelet count less than 80,000 cells/mcL, reticulocyte count less than 80,000 cells/mcL (if hemoglobin is less than 9 g/dL), and hemoglobin less than 4.5 g/dL.[2,6,15,21] If during any point in treatment the patient's blood levels fall into the toxic ranges, hydroxyurea is temporarily withheld, and blood levels are monitored weekly until they reach the accepted ranges.

The most common and earliest toxic blood levels to present include neutropenia, followed by reticulocytopenia. These two blood parameters are used mostly to indicate toxicity and guide dosing.[2,21] After recovery, the patient can be restarted on hydroxyurea at a dose 5 mg/kg/day less than that associated with hematologic toxicity and can resume escalation every 8 weeks as long as blood levels are acceptable.[2,15]

Long-term therapy is indicated for patients who improve while taking hydroxyurea. Because clinical responses to treatment may take up to 6 months, a 6-month trial on the maximum tolerated dose is required before considering discontinuation due to treatment failure.[2]

TABLE 2. Selected acute SCD-related complications[2]

Complication	Definition/clinical picture
Acute anemia	Acute decrease in hemoglobin of ≥2 g/dL below the patient's baseline value
ACS	A new pulmonary infiltrate on chest radiograph **AND** A combination of chest pain, fever, tachypnea, wheezing, cough, or retractions*
Acute splenic sequestration	Increase in palpable spleen size of 2 cm or more below costal margin from previous examination **AND** Decrease in hemoglobin of 2 g/dL or more (or 20% or more) from steady-state values
Acute hepatic sequestration	Liver enlargement below the right costal margin of 3 cm or more for children or 5 cm or more for adults from previous examination **AND** Decrease in hemoglobin of 2 g/dL or more over a few hours to days

*The clinical picture of pneumonia in a person with SCD usually fulfills the criteria for ACS.

Initial laboratory tests and monitoring Baseline laboratory work and continued monitoring must be done to ensure that patients' blood counts remain above the toxic levels (**Table 4**).[2,11,21] The frequency of monitoring depends on the phase of treatment, with more frequent laboratory draws during the dose escalation phase, and less frequent draws once the patient has reached the maximum tolerated dose (**Table 4**). PCPs should communicate with the hematology specialists concerning the recommended monitoring schedule. PCPs also should be aware of the blood levels that are considered toxic and report these to the hematology specialist.

Benefits of hydroxyurea The benefits of hydroxyurea use are numerous. In adults, for example, the drug has been shown to reduce vaso-occlusive episodes from an average of 4.5 to 2.5 per year, reduce the episodes of acute chest syndrome (51% less than placebo), and reduce the number of transfusions (34% less than placebo).[2] Similar findings have been seen in children, as hydroxyurea has been shown to reduce vaso-occlusive episodes by 36%, episodes of acute chest syndrome by 43%, ED visits by 43%, hospitalizations by 47%, and blood transfusions by 57%.[22] In select populations, hydroxyurea also has been shown to help prevent primary stroke.[23] Most importantly, hydroxyurea has been shown to reduce mortality in adults and children (40% reduced mortality in adults, and 99.4%

TABLE 3. NHLBI health maintenance recommendations for patients with SCD[2]

Further details for each recommendation can be found at www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf.

Health maintenance	Rationale	Recommendation(s)
Prevention of invasive infections	Due to defective or absent splenic function, children with SCA have a very high risk for septicemia and meningitis in the absence of appropriate prophylaxis	• Administer oral penicillin prophylaxis (125 mg for children under age 3 years and 250 mg for age 3 years and older) twice daily until age 5 years in all children with SCA. • Remind patients with SCD, their families, and caregivers to seek immediate medical attention whenever fever occurs (temperature greater than 101.3° F or 38.5° C), due to the risk for severe bacterial infections. • All patients with SCD should be immunized as recommended by the Advisory Committee on Immunization Practices (ACIP), including the ACIP recommendations for additional pneumococcal and meningococcal vaccines in patients with SCD.*
Screening for renal disease	Sickle cell nephropathy is a major complication of SCD	• Screen all patients with SCD for proteinuria, beginning by age 10 years, and repeat screening annually. • If positive, perform a first morning void urine albumin-creatinine ratio and if abnormal, consult with or refer to a renal specialist.
Screening for retinopathy	All individuals with SCD are at risk for retinal disease	• Refer patients with SCD to an ophthalmologist for a dilated eye examination to evaluate for retinopathy every 1 to 2 years, beginning at age 10 years. • Refer patients with suspected retinopathy to a retinal specialist.
Screening for risk of stroke using neuroimaging	Stroke is one of the most common and devastating complications of SCA	• Screen annually with transcranial doppler, beginning at age 2 years and continuing until at least age 16 years. If results are conditional (170–199 cm/s) or elevated (>200 cm/s), refer patient to a specialist with expertise in chronic transfusion therapy. • Do not perform screening with transcranial doppler in children with genotypes other than SCA. • Do not perform screening with CT or MRI in asymptomatic children with SCD. • Do not perform screening with neuroimaging (transcranial doppler, CT, or MRI) in asymptomatic adults with SCD.
Screening for pulmonary disease	Respiratory conditions in children and adults with SCD are associated with an increased risk of mortality	• In children and adults with SCD, assess for signs and symptoms of respiratory problems (such as asthma, chronic obstructive pulmonary disease, restrictive lung disease, or obstructive sleep apnea) by history and physical examination. • If respiratory problems are suspected, further assessment, including pulmonary function tests, is recommended to determine the cause and develop a plan to address the problem. • Do not perform screening with pulmonary function tests in asymptomatic children and adults with SCD.
Reproductive counseling	SCD increases the risk for complications in both the mother and the fetus	• Encourage patients affected by SCD to have a reproductive life plan. • As a part of primary care visits, provide risk assessment and educational and health promotion counseling (or refer to individuals with expertise in these disciplines) to all women and men of childbearing age. • Provide contraceptive counseling, if desired, to prevent unintended pregnancy, and if pregnancy is desired, provide preconception counseling. • If the partner of an individual with SCD has unknown SCD or thalassemia status, refer the partner for hemoglobinopathy screening. After testing, refer couples who are at risk for having a potentially affected fetus and neonate for genetic counseling. Specific recommendations for women with SCD • Test women who have been transfused and are anticipating pregnancy for red cell alloantibodies. If positive, test their partners for the corresponding red cell antigen(s). • If the partner tests positive for the corresponding red cell antigen(s), counsel the couple about the risks of hemolytic disease in the fetus and neonate, and how it is monitored and treated, or refer them to a maternal-fetal specialist who can provide this education. • Counsel women with SCD and their partners or refer for counseling about the increased risks of adverse pregnancy outcomes, including intrauterine growth restriction, preterm delivery, and stillbirth. Additional fetal surveillance is required during a pregnancy. Women also should be counseled on the increased risks to their health during pregnancy, including an increased frequency of pain crises, thrombosis, infections, preeclampsia, and death.
Contraception use	Additional considerations need to be taken into account when assessing the safety of contraceptive methods in women with SCD, such as a history of stroke as a contraindication to combined hormonal contraception	• Progestin-only contraceptives (pills, injections, and implants), levonorgestrel intrauterine devices, and barrier methods have no restrictions or concerns for use in women with SCD. • If the benefits are considered to outweigh the risks, combined hormonal contraceptives (pills, patches, and rings) may be used in women with SCD.

*Vaccine recommendations and schedules can change frequently; follow the most up-to-date schedule. Detailed recommendations for vaccination of patients with functional or anatomic asplenia (such as in SCD), including catch-up schedules, can be found at www.cdc.gov/vaccines/schedules.

15-year survival rate in children taking the drug versus 95.4% in children not taking it).[2,24]

Adverse reactions Transient cytopenias have been the most observed adverse reaction; however, they typically resolve within 1 week after withholding hydroxyurea.[21] Although the guidelines do not recommend any formal screening schedules, clinicians should use common practice knowledge to look for signs of infections, such as tuberculosis, that may be worsened with myelosuppression.

Increased cancer risk also is a concern; some reports have suggested that hydroxyurea increases the risk for secondary malignancies in patients taking hydroxyurea for myeloproliferative neoplasms such as polycythemia vera or essential thrombocythemia.[6] However, these cases have only been seen in patients taking hydroxyurea for myeloproliferative disorders, in which secondary leukemias were a concern regardless of hydroxyurea use.[6] To date, there have been no findings of increased incidences of cancer in patients taking hydroxyurea for SCD.[25]

Although the data are limited in humans and the quality of evidence is very low, no clearly defined risk of infertility or teratogenicity has been found with hydroxyurea use.[2,6] Until further research, the NHLBI guidelines recommend that patients should be counseled about the need for contraception while taking hydroxyurea, and that the drug should be discontinued in patients who are pregnant or breastfeeding.[2] Lastly, current literature shows no increased risk of administering live-virus vaccines to patients taking hydroxyurea. The benefits continue to outweigh the risks, and routine vaccination, including live-virus vaccines, should be offered.[26]

OTHER DISEASE-MODIFYING THERAPIES

Hematopoietic stem cell transplantation The only potentially curative therapy available for SCD is hematopoietic stem cell transplantation (HSCT or HCT). This procedure is restricted to a small number of patients because of its high cost and the limited number of patients with histocompatible donors (fewer than 25%).[27] Adverse reactions include graft-versus-host disease, gonadotoxicity, and associated risk of infertility.[2,27]

Chronic transfusion therapy By maintaining low levels of sickled erythrocytes, chronic transfusion therapy can reduce or prevent SCD-related complications. Commonly recognized indications for transfusion therapy, as stated in the NHLBI guidelines, include prevention of primary stroke in at-risk children and prevention of secondary stroke in patients who already have had a stroke. Transfusion therapy must be used appropriately because chronic transfusions can lead to significant complications, such as allo- and autoimmunization, immune-mediated hemolysis, hyperviscosity, and iron overload.[2]

> Health maintenance interventions and disease-modifying therapies can improve patient quality of life.

l-glutamine This oral medication was approved by the FDA for the reduction of acute complications of SCD in patients age 5 years and older.[28] The mechanism of action is not fully understood but l-glutamine is thought to protect erythrocytes from oxidative damage.[28] l-glutamine has been shown to decrease painful episodes, acute chest syndrome episodes, and hospitalizations.[29] Some limitations to its use include cost (more expensive than hydroxyurea), limited data showing benefits, and the lack of long-term studies demonstrating continued safety and efficacy.[28]

TABLE 4. Laboratory testing for patients during hydroxyurea treatment[2,11,21]

Baseline tests

- CBC count with WBC differential and reticulocyte count. Consider serum iron, total iron binding capacity, ferritin, B-12, and folate based on RBC mean corpuscular volume findings because hydroxyurea-induced macrocytosis may mask deficiency anemias.
- Comprehensive metabolic panel including renal (blood urea nitrogen, creatinine) and liver (alanine aminotransferase, bilirubin) function tests
- Quantitative measurement of HbF (hemoglobin electrophoresis or high-performance liquid chromatography)
- Pregnancy test in women

Monitoring tests

Test	During dose escalation	At maximum tolerated dose
CBC count with WBC differential	At least every 4 weeks	Every 2-3 months
Comprehensive metabolic panel including renal and liver function tests	Every 2 months	Every 3-6 months
Quantitative measurement of HbF	Every 3-6 months	Every 3-6 months

EMERGING THERAPIES

Medications such as the monoclonal antibody crizanlizumab, which target the cell adhesion molecule p-selectin, have shown potential.[30] Promising research on gene therapy as a cure for SCD is underway.[31]

CONCLUSION

SCD is a chronic disorder with high morbidity and mortality. However, interventions such as health maintenance and disease-modifying therapies can improve patient quality of life. PCPs can become more involved in the care of these patients by familiarizing themselves with SCD and its complications, implementing the NHLBI health maintenance recommendations, having an understanding of the available therapies, particularly hydroxyurea, and helping to monitor its use. **JAAPA**

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