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Sickle cell disease: Where are we now?

By Vincent M. Vacca, Jr., MSN, RN, CCRN, SCRN, and Lora Blank, MSN, RN

SICKLE CELL DISEASE (SCD) is a group of inherited red blood cell (RBC) disorders that cause the production of abnormal hemoglobin (Hb), the oxygen-carrying component of the RBC. SCD is a chronic disease that can cause many systemic complications, such as organ dysfunction and infection due to inadequate tissue perfusion and oxygenation.

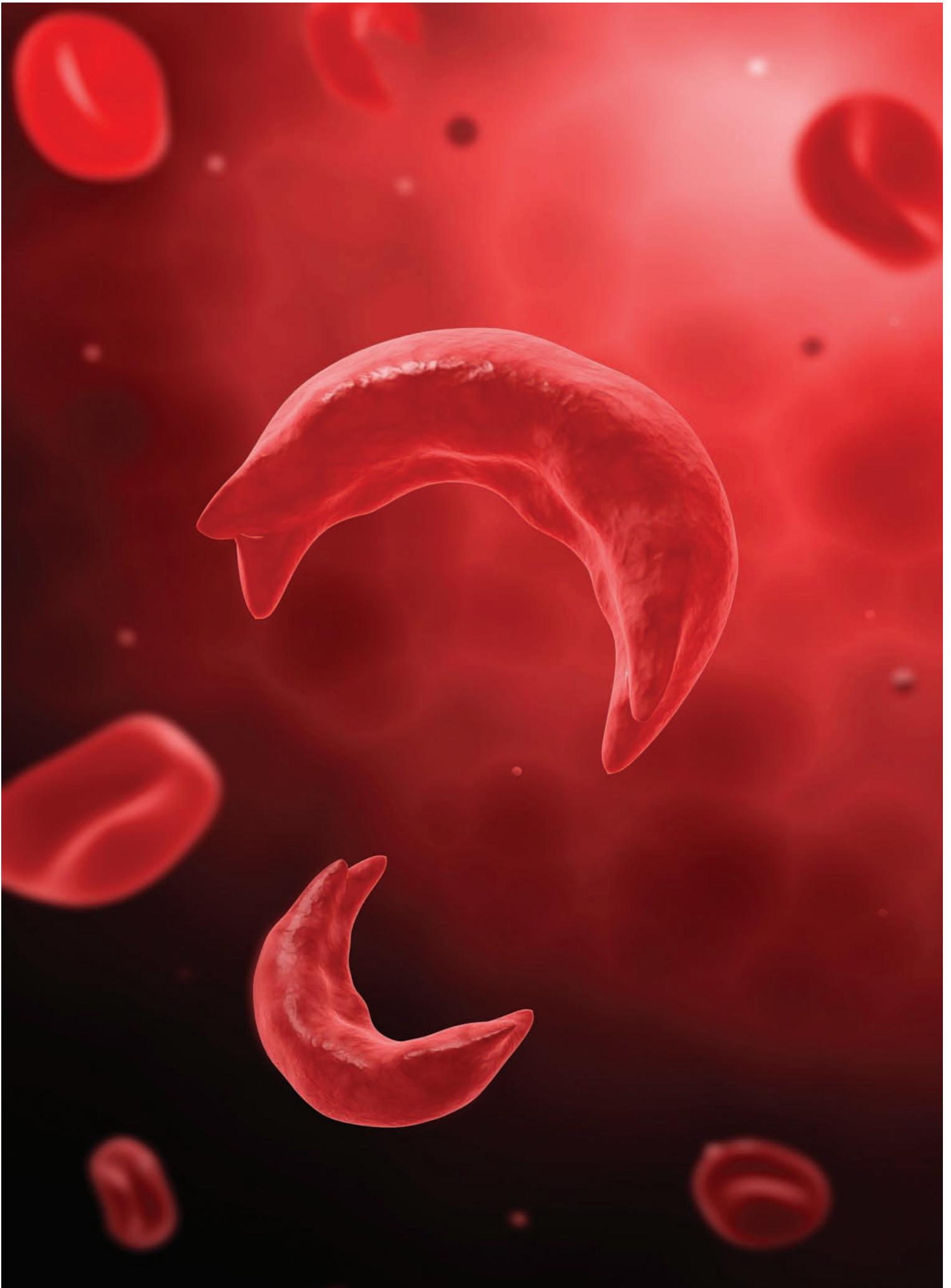
This article presents an overview of signs and symptoms, complications, and current treatment options.

SCD versus sickle cell trait

It's important to distinguish between SCD and sickle cell trait. In all forms of SCD, the affected person has inherited at least one abnormal sickle cell Hb gene "S" (HbS) from one parent plus another abnormal Hb gene from the other parent.

In the most common and severe form of SCD, type HbSS sickle cell anemia, the person has inherited two sickle cell genes ("S"), one from each parent. In other types of SCD, which vary in incidence and severity, in addition to the abnormal sickle cell Hb "S" gene, the person has inherited another abnormal gene (C, D, E, O, beta-zero [B⁰] thalassemia, or beta-plus [B⁺] thalassemia).¹

Unlike those with SCD, who have inherited two abnormal Hb genes, people with sickle cell trait (SCT) have inherited one sickle cell Hb gene "S" from one parent plus one normal Hb "A" gene from the other parent. (See *Understanding SCD inheritance*.) The person with SCT is designated as type HbSA. The person with SCT rarely has sickle cell-related health problems and can expect



to live a normal lifespan but may pass the SCT along to children. This is an important distinction.²

Prevalence

SCD is the most common inherited RBC disease in the United States.³ For decades, SCD was considered a children's disease because few patients survived to adulthood. By 1980, however, 50% of children with SCD survived to age 20. Today, the average life expectancy ranges from 40 to 60.⁴

Most of those affected are of African ancestry; a minority are of Central or South American, Middle Eastern, Mediterranean (Turkish, Italian, Greek), or Asian Indian heritage.⁵ According to the CDC, SCD occurs in about 1 in 365 Black American births and in 1 in 16,300 Hispanic births, and affects 100,000 Americans.⁴

In the United States, newborns are routinely screened for SCD. Prenatal diagnosis using amniocentesis can be used to test amniotic fluid for the sickle cell gene.⁶ (See *SCD by the numbers*.)

Pathophysiology

The abnormal sickle Hb in SCD is less soluble than normal fetal or adult Hb.^{7,8} When the oxygen level and pH in blood is low, intracellular changes

occur and the HbS adopts a crystal-like formation, causing the RBC to lose its round, pliable, biconcave disc shape and become deformed, rigid, and sickle- or crescent-shaped.⁸ The sickled RBCs become more adherent; their ability to change shape as they move through the circulation (deformability) diminishes and the permeability of the RBC membrane is increased.⁸⁻¹²

Blood viscosity also increases through a combination of intrinsic properties and abnormal interactions of sickled RBCs with leukocytes, platelets, vascular endothelium, and clotting factors. The lack of deformability and enhanced stickiness of sickled RBCs causes them to clump to each other, adhere to vascular endothelium, and obstruct the vessel lumen.⁸

The sickling process occurs over time; if the RBC is exposed to adequate amounts of oxygen before the membrane becomes too rigid, it can revert to a normal shape. If not, then clumping of sickled RBCs leads to vascular occlusion and diminished tissue perfusion, causing complications such as pain, end-organ ischemia, and infarction.¹³ (See *Picturing sickle cell crisis*.)

SCD by the numbers

Estimates from The World Health Organization are that over 310,000 people are born each year with SCD, mostly in sub-Saharan Africa.⁴¹ The expected incidence of SCD is 1 in 625 births. However, due to increases in migration, SCD is becoming more common worldwide. Approximately 25 to 30 million people worldwide have SCD, with about 100,000 of them living in the United States.^{8,9,39,42}

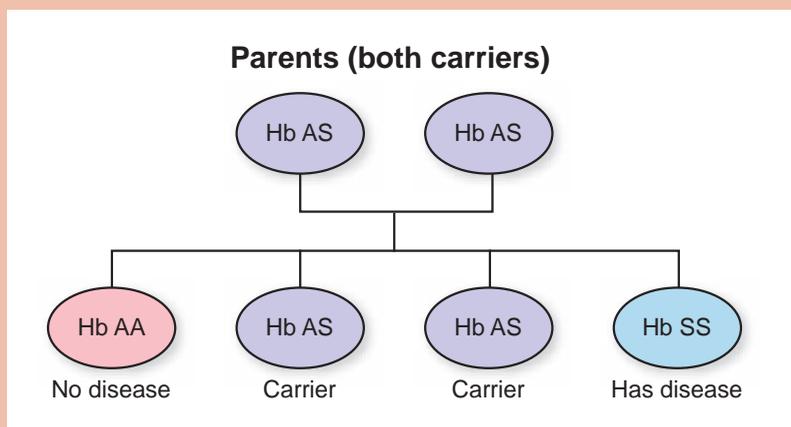
Sickle cells are also fragile and rapidly destroyed by mechanical forces as they circulate. While normal RBCs live 90 to 120 days, the life of a sickle cell is only 10 to 20 days. The destruction of RBCs faster than the bone marrow can replace them results in hemolytic anemia and severely compromises the blood's oxygen-carrying capacity.¹³

The primary manifestations of SCD are chronic hemolytic anemia and acute vaso-occlusive crisis (VOC), which are mainly characterized by ischemic-reperfusion tissue injury.^{14,15} SCD is characterized by acute and chronic vaso-occlusion that can cause acute painful episodes, acute chest syndrome, organ damage, stroke, and even death.¹³

SCD vaso-occlusion

Sickled RBCs adhere to blood vessel walls causing macro- and microvaso-occlusion (VO). VO, along with hemolytic anemia, causes hypoxia, acidosis, inflammation, ischemia, and tissue infarction. Hypoxia further increases RBC sickling, worsening and perpetuating VO. A prothrombotic state resulting from thrombin activation, decreased levels of circulating anticoagulants, impaired fibrinolysis, and platelet activation are also involved in the pathogenesis of VO.¹⁶ As a result of VO, patients are at significant risk for end-organ damage and other complications. Cardiovascular, pulmonary, and other complications associated with VO are major causes of morbidity and mortality for all individuals with SCD.^{9,17} (See *Common complications of SCD*.)

Understanding SCD inheritance



Source: Kyle T, Carman S. *Essentials of Pediatric Nursing*. 3rd ed. Philadelphia, PA: Wolters Kluwer; 2017.

VO also causes acute pain episodes, termed *vaso-occlusive crisis* (VOC).¹⁸ VOC is the most common cause of hospitalizations for patients with SCD. The pain associated with VOC results from inflammatory mediators released from damaged RBCs, macrophages, mast cells, and platelets activating nociceptive pain receptors.¹⁹⁻²¹

Conditions that can trigger a VOC include infection, pregnancy, alcohol or tobacco use, exposure to temperature extremes, dehydration, exposure to high altitudes, extreme physical exertion, and stress; however, often no trigger can be identified.¹⁹⁻²¹

The pain is sudden and typically manifests in the lower back, in one or more joints, and/or in the extremities. The pain may be localized or migratory and is typically described as continuous and throbbing. The pain can cause patients to grunt, groan, cry, twist, turn, and assume abnormal postures in an attempt to obtain relief. The combination of hypoxia, reperfusion injury, inflammation, and ischemic tissue damage is what makes the VOC-associated pain experience of SCD unique.¹⁹⁻²¹

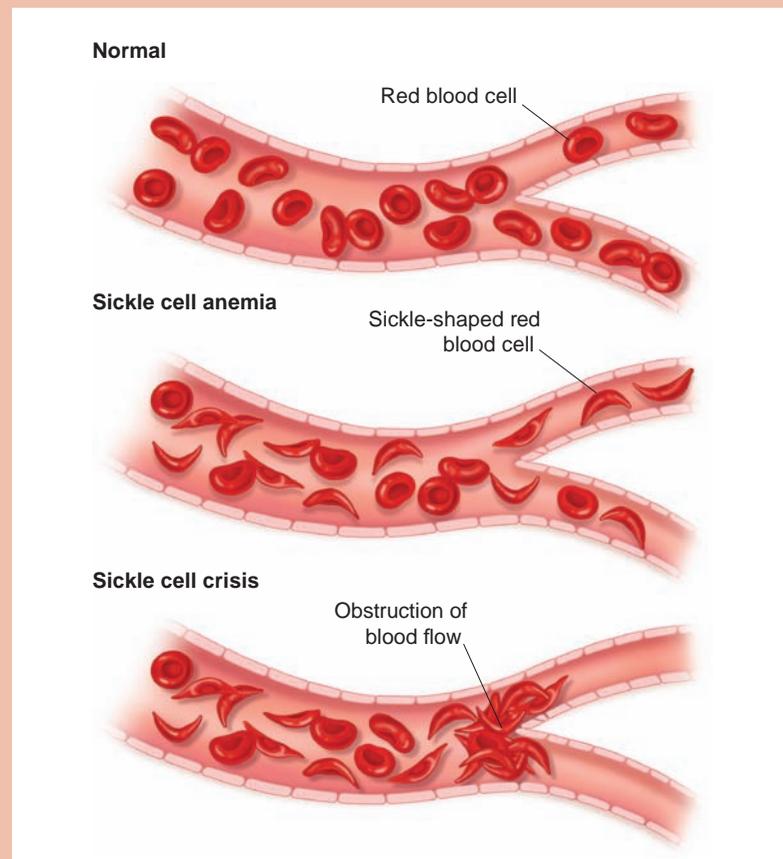
VOC episodes can occur from the first year of life onward, causing injury and permanent damage to tissues and organs. Due to the chronic nature of SCD, the severity and frequency of pain crises wax and wane, relapse, and can recur unpredictably. Each instance of painful crisis is associated with residual inflammatory damage that accumulates and can lead to organ dysfunction and even organ failure.¹⁹ The pain from VOC may last hours to days. The number of pain crises per year varies widely, with some patients experiencing a constant low level of pain.

SCD treatment

Goals of SCD management include maximizing tissue oxygenation/perfusion, preventing and treating complications associated with anemia

Picturing sickle cell crisis

The sickle (crescent-shaped) blood cells indicate sickle cell anemia. Sickle cell crisis causes obstruction of blood flow and pain.



Source: Creason C. *Stedman's Medical Terminology*. 2nd ed. Baltimore, MD: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.

and VO, preventing and aggressively treating infection, and managing pain.^{8,22} SCD is a chronic disease.

Oral hydroxyurea. Long-term oral hydroxyurea (HU) administration reduces or prevents many acute and chronic complications of SCD.²³ HU is rapidly absorbed, has near-complete bioavailability, and is therapeutic with once-daily oral dosing.⁸ Decades of research have established that the most effective treatment for SCD is to increase circulating normal or fetal hemoglobin (HbF) and reduce HbSS. Increasing the concentration of HbF is the primary effect of HU. Other benefits of HU include lowering the number of circulating leukocytes and reticulocytes and

decreasing their adhesiveness, which can reduce vascular occlusion leading to VOC. HU also increases RBC size and improves cellular deformability, which increases blood flow and reduces VO. Nitric oxide, a vasodilator, is released directly from HU metabolism and may contribute to local vasodilation. HU therapy substantially reduces the frequency of painful episodes associated with VOC and the need for transfusions and hospitalizations.^{17,24,25}

Although HU isn't as effective as blood transfusion therapy in preventing stroke or VOC, it's the most widely used therapy and has proven efficacy in children and adults with SCD. HU is the only FDA-approved

pharmacologic treatment for induction of HbF in adults with SCD, and it's also approved by the European Medicines Agency for both children and adults with SCD. The benefit is directly related to the amount of HbF produced in response to the drug. However, several clinical studies have shown that individual responses to HU treatment vary. Induced HbF levels range from 10% to more than 30% even for patients on similar dosing regimens.⁸

HU therapy is indicated for children 5 years and older who have severe complications of SCD. It's recommended for children as young

as 9 months, even those without symptoms, and for children as young as 18 months who have frequent pain, severe symptomatic anemia, or severe vaso-occlusive events. Monitor CBC counts regularly in patients on HU therapy for evidence of immunosuppression such as leukopenia.^{8,23} Monitor CBC counts at least every 4 weeks when the patient's dosage is being adjusted.⁸

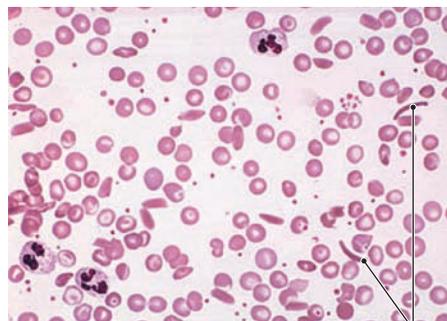
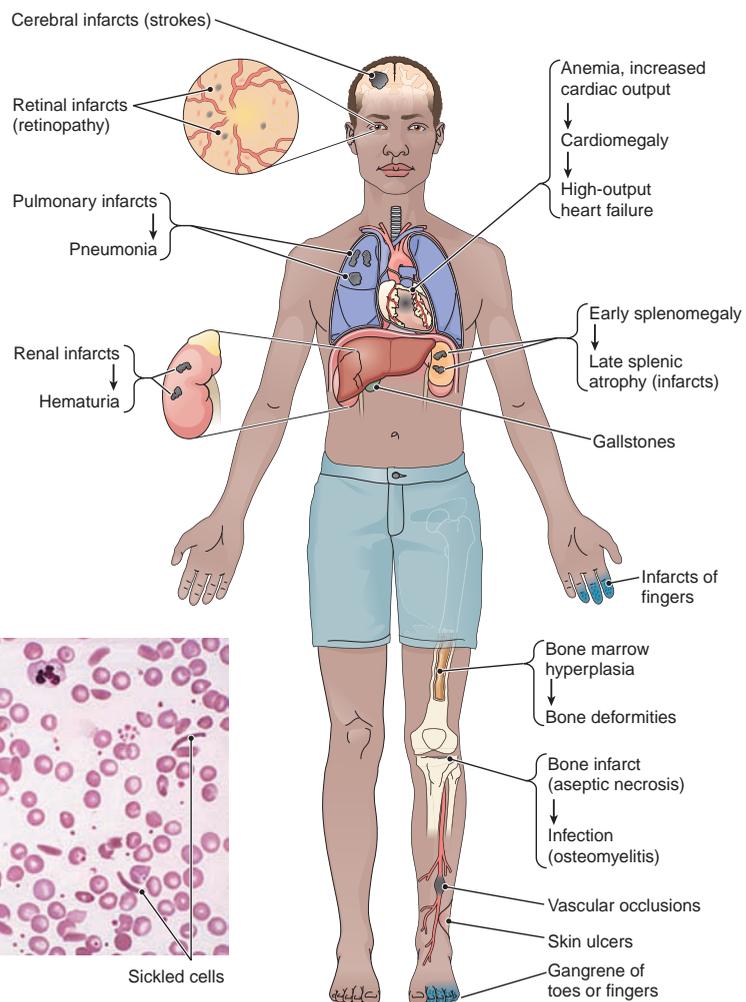
Adverse reactions and safety issues associated with long-term use of HU aren't known. But patients with SCD who have higher levels of circulating HbF have less pain, lower morbidity, and improved survival.^{25,26}

To abort VOC at its prodromal stage, a trial of hydration, anti-inflammatories, analgesics, and possibly vasodilators can be instituted. Treatment for patients experiencing VOC includes therapy to interrupt the pain episode and limit tissue and organ damage. Pain interventions include nonsteroidal anti-inflammatory drugs for mild to moderate pain if not contraindicated, and opioids such as morphine for more severe pain. Treating acute pain quickly and aggressively may help to head off chronic pain and improve quality of life. Treatment should be based on the patient's self-reported pain

Common complications of SCD

SCD causes complications due to impaired tissue perfusion from vascular occlusions and anemia. End-organ damage and death may result. Common complications of SCD include:

- stroke
- hypertension
- ischemic cardiomyopathy
- pulmonary hypertension
- chronic kidney disease
- liver and gallbladder disease
- splenic disorders (which increase infection risk)
- skeletal abnormalities and joint damage
- retinopathies
- lower extremity chronic venous disease (secondary to venous hypertension and/or deep vein thrombosis)
- acral erythema (hand-foot syndrome)
- priapism
- delayed growth and delayed puberty.



Sickled cells

Source: McConnell TH. *The Nature of Disease: Pathology for the Health Professions*. 2nd ed. Baltimore, MD: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014.

intensity rating and what's been used successfully in the past.^{8,18}

Blood transfusion therapy. The decision to transfuse blood should be based on a risk-benefit assessment, usually after consultation with an expert such as a hematologist.⁸ Because sickled RBCs promote VO, normal donor blood is transfused to suppress that process. Blood transfusion replaces abnormal HbS with normal hemoglobin (HbA) to interrupt a VOC by increasing perfusion and subsequently cellular oxygen delivery.^{3,17,27} Blood transfused every 3 to 4 weeks raises HbA concentration, reduces HbSS, which improves blood flow with nonsickled RBCs, and suppresses production of sickled RBCs. The optimal level to raise the HbA with blood transfusion isn't known, but an effective therapeutic target for transfusion therapy is to maintain HbS at less than 30% of total Hb.²⁸

Blood transfusion therapy requires patient education, awareness of the benefits and risks, informed consent, establishment of appropriate and adequate vascular access, and preparation for and administration of multiple units.

Investigational therapies. Presently, the only cure for SCD is through hematopoietic cell transplantation (HCT). HCT is an evolving treatment with many complications and is limited to children age 16 or younger with severe signs and symptoms who are unresponsive to HU and transfusion therapy and who have a sibling-matched donor.²⁹ Ongoing investigations using gene therapy to insert corrective genes into bone marrow also show promise.³⁰

Complications

• **Blood transfusions** are associated with several possible risks, including hyperviscosity, alloimmunization, hemolysis, and iron overload. Transfusions, whether administered sporadically or regularly, present a

substantial iron load to the recipient. Because transfusions introduce iron outside the normal pathways of iron regulation, this can overload the normal physiologic ability to process iron and can lead to iron overload and subsequent organ dysfunction. Although iron overload related to the number of transfusions and transfusion method is possible, it can be managed with iron chelation therapy.^{8,10,31}

Other potential risks associated with blood transfusion include increased viscosity due to a higher Hb content, which could trigger VO and a painful VOC. Delayed hemolytic transfusion reaction can develop 7 to 28 days after RBC transfusions due to blood group incompatibilities. Transfusion reactions should be considered for patients with worsening anemia, jaundice, or pain after transfusion.⁸

• **Infection prevention and treatment.** Patients with SCD are highly vulnerable to infection, and infections tend to be more severe than in those without SCD. This is largely due to dysfunction of the spleen from microinfarcts secondary to VO that developed in childhood. The spleen is responsible for blood filtration and antibody production, so a nonfunctioning spleen, or *asplenia*, increases the risk of infection. By age 1 year, 30% of pediatric patients with SCD are asplenic, and by age 6 years, 90% are asplenic. The infection risk for children with SCD is 400 times higher compared with the general population. Guard these patients against infection and maintain current influenza, pneumococcal, and meningococcal immunizations in addition to recommended routine childhood immunizations.^{8,15,17,32}

Children with SCD typically receive prophylactic antibiotic therapy (usually penicillin or an alternative) until at least age 5 years. Besides other routine immunizations, adults with SCD should receive influenza and pneumococcal immunizations.²²

Immunization history and status should be reviewed at each health-

care visit. Teach adults, children, and families that fever (greater than 38.5° C or 101.5° F) is a medical emergency requiring prompt evaluation, blood cultures, and treatment including antibiotics.³³

All patients with SCD must maintain adequate hydration to reduce SCD complications. Patients who can't drink adequate fluids may need I.V. therapy. The patient's fluid volume status and potential for blood transfusion determine the selection of I.V. fluids. Because patients with SCD may have a decreased ability to excrete sodium, nurses must monitor sodium levels and watch for hypernatremia, especially in patients receiving 0.9% sodium chloride I.V. solution. Hypernatremia can dehydrate RBCs and increase sickling.²⁹

Because patients with SCD are hypercoagulable, hospitalized adults with acute medical illness should receive venous thromboembolism prophylaxis unless contraindicated.^{29,34}

• **SCD and stroke.** Strokes are a devastating neurologic manifestation and cause substantial morbidity in patients with SCD.^{8,20,24}

Ischemic strokes in SCD are more common in children and older adults, and least common in adults ages 20 to 29.⁸

Patients experiencing strokes commonly present with signs and symptoms including facial droop, dysarthria or aphasia, upper extremity paresis, and balance and visual disturbances, which may be preceded by transient ischemic attacks. Patients with silent cerebral infarcts can present with nonfocal neurologic signs such as developmental delays, poor or declining school performance in children, or changes in social, role, or work functioning in adults. Throughout their lives, patients with SCD should be considered for formal neurocognitive evaluation when assessments reveal any of these concerns.⁸

For patients with a neurologic deficit suggesting an acute evolving

What's the STOP study?

The Stroke Prevention Trial in Sickle Cell Anemia (STOP) represented a significant advance in screening for stroke in patients with SCD. STOP demonstrated the efficacy of transcranial Doppler (TCD) screening for identifying children at high risk for ischemic cerebral injury, including stroke.^{43,44}

The STOP clinical trial studied children with abnormal TCD velocities, defined as 200 cm/s and higher, who were randomly assigned to regular blood transfusion every 3 to 4 weeks or standard care, which meant no transfusion or only episodic transfusions. The risk of stroke was reduced dramatically in the transfused group.^{44,45} Blood transfusion therapy for patients with SCD who have abnormal TCD velocities can reduce the risk of stroke from 10% per year to less than 1%, leading to a 90% reduction of stroke risk.^{8,10,45}

TCD is recommended at least yearly in children, and blood transfusion therapy should be offered when cerebral blood flow velocity reaches or exceeds the 200 cm/s threshold. This approach, known as the *STOP protocol*, has been universally endorsed as a standard of care for children with SCD ages 2 to 16 years.^{44,45}

The STOP trial demonstrated the efficacy of long-term periodic blood transfusions for primary stroke prevention. STOP investigators found no evidence, despite regular monitoring, that any transfusion-borne infections were associated with the preventive transfusions given during the trial.

ischemic stroke, a blood transfusion, including a complete exchange transfusion, may be indicated.²⁴ The stroke recurrence rate in the first 2 years is approximately 50% if no treatment is initiated.²⁴ By reducing abnormal HbSS and increasing normal HbA, blood transfusion therapy is indicated as both a treatment for acute evolving ischemic stroke and as a preventive measure for ischemic stroke when used with TCD assessment.^{21,24,28} (See *What's the STOP study?*)

Hemorrhagic stroke is most common in patients with SCD who are ages 20 to 29. Because of its unique pathology, hemorrhagic stroke carries a higher risk of death than ischemic stroke. Risk factors for hemorrhagic stroke associated with SCD include low Hb, leukocytosis, a blood transfusion within the last 14 days, treatment with corticosteroids, and VOC. Keep in mind that the presence of a hemorrhagic stroke in SCD doesn't exclude the possibility of coexisting past or acute evolving ischemic stroke.²⁴

In SCD, HbS leads to a severe cerebral vasculopathy causing micro- and macrovessel occlusion and sub-

sequent development of collateral vessels around the arterial circle of Willis (COW). The COW is located at the base of the brain. The cerebral vasculopathy affecting the COW leads to a condition called *moyamoya syndrome*, a Japanese word defined as a "puff of smoke." It's used to describe the angiographic appearance of collateral vessels that arise from the COW due to occlusions involving these vessels. Although moyamoya syndrome occurs in people without SCD, studies have shown that the presence of moyamoya significantly increases the risk of hemorrhagic stroke, especially for those with SCD. Although both ischemic and hemorrhagic strokes are possible, intracranial hemorrhage is more common in

adults with SCD and moyamoya syndrome.^{35,36}

The signs and symptoms of hemorrhagic stroke include sudden severe headache, nausea, vomiting, and rapid deterioration of neurologic function, which can progress to coma. Transient motor or sensory symptoms may occur similar to seizure activity.

Additional management of patients with hemorrhagic stroke includes the discontinuation of any anticoagulants and antiplatelet agents. A reversal agent may be needed for some types of anticoagulation therapy. Angiography may be used to identify the vessels involved and guide therapy. Neurosurgical evaluation and intervention may be needed to reduce intracranial pressure or treat a ruptured cerebral aneurysm.

Nursing interventions for patients with SCD

- Assess vital signs and grade the amplitude of peripheral pulses, presence of pain, skin color and temperature, capillary refill time, and skin integrity.
- Initiate RBC transfusions as indicated.
- Assess for impaired gas exchange due to decreased oxygen-carrying capacity of the sickled RBCs. Perform a detailed and comprehensive pulmonary assessment including breath sounds, respiratory rate, and oxygenation. Assess for abnormal findings such as dyspnea, orthopnea, cough, decreased PaO₂, oxygen saturation less than 90%, presence of cyanosis, and abnormal breath sounds such as

Understanding acute chest syndrome

Acute chest syndrome is another common and serious acute complication of SCD. Clinically, although acute chest syndrome can develop at any time, it usually presents as a sudden onset of some combination of cough, shortness of breath, retractions, and crackles that are accompanied by a new pulmonary infiltrate on chest radiograph. Children usually have a fever and upper- or middle-lobe involvement, but many adults are afebrile and have multilobe disease. Acute chest syndrome has no distinctive lab features, but hemoglobin concentration often declines sharply. Because it's a major cause of death in patients with SCD, patients with this syndrome should receive prompt diagnosis and treatment.^{8,46}

crackles and wheezes. Assess for chest pain, which may signify acute chest syndrome. (See *Understanding acute chest syndrome*.) Monitor the patient for any symptom progression. Initiate oxygen therapy, bronchodilators, and inhaled steroids as needed.

- Assess the patient for alterations in fluid volume and for signs and symptoms of fluid volume deficit and abnormal renal function (often secondary to microangiopathy). Assess for signs and symptoms of dehydration, such as dry skin and mucous membranes, decreased skin turgor, hypotension, and tachycardia. Monitor urine output, urine specific gravity, blood urea nitrogen and creatinine levels, and serum electrolyte levels. Initiate I.V. fluid therapy if needed.
- Examine the patient's skin, noting the presence of any wounds or edema. Initiate wound care if needed and measures to prevent skin breakdown.
- Perform a careful pain assessment, including the type, intensity, location, pain triggers, and ongoing evaluation of pain relief measures.^{21,24,35,37,38}

Patient teaching

Patients need to know how to manage chronic disease and prevent complications. Teaching points include the genetic implications of the disease, such as family planning. Stress the importance of regular follow-up with healthcare providers expert in SCD management and of obtaining lab tests as prescribed. Encourage optimal self-care, including taking prescribed medications, reporting any over-the-counter medications or supplements before taking them, having regular dental and eye examinations, maintaining good nutrition and adequate hydration, avoiding extreme temperatures and physical exertion, identifying and avoiding VOC triggers, and avoiding smoking and alcohol consumption. With the patient, develop an individualized plan for managing pain at home and teach the patient to begin treatment



Bonus content!

Head to www.nursing2017.com for more information about managing pain in patients with sickle cell disease.

Acute vaso-occlusive crisis in patients with sickle cell disease

http://journals.lww.com/nursing/Fulltext/2017/01000/Acute_vaso_occlusive_crisis_in_patients_with.19.aspx

as soon as a VOC episode seems to be starting.³⁹ Promote infection prevention strategies including obtaining all recommended immunizations, and avoiding contact with others who have infections; taking all prescribed doses of antibiotics as directed; and protecting skin from injury. Provide information about pain management interventions, assessment, and plans. Advise the patient to immediately seek medical attention for fever or any sign of infection (such as erythema, edema, or cough); severe joint or other pain; chest pain; decreased or cloudy, bloody, or dark urine; any vision changes; and any changes in neurologic status.⁸

Advances made, more needed

Over the past 20 years, the understanding of the pathophysiology and management of SCD has increased significantly. SCD can now be managed successfully using evidence-based screening and treatment guidelines. Despite recent progress, however, patients with SCD continue to experience challenges in maintaining quality of life and a shorter-than-normal lifespan.^{24,40} Better treatments and a potential cure for SCD may come from ongoing research. ■

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At Brigham and Women's Hospital in Boston, Mass., Vincent M. Vacca, Jr., is a clinical nurse educator and Lora Blank is an RN in the neuroscience ICU.

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