

## EDUCATIONAL OBJECTIVES

After completing this continuing education activity, pharmacists will be able to

- Describe SCD's different phenotypes and implications for therapy
- Classify the new therapies for adult and pediatric SCD patients
- Describe the pharmacist's responsibilities and opportunities in management of SCD patients
- Review investigational agents in the pipeline for SCD

After completing this continuing education activity, pharmacy technicians will be able to

- Compare the cost savings of newer agents to the standard of care—hydroxyurea
- Describe SCD's different phenotypes and implications for therapy
- Determine when to refer patients to the pharmacist for recommendations or referrals



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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## You Asked for It! CE



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## SICKLE CELL DISEASE: Dispelling Myths, Making Clinical Progress

**ABSTRACT:** Sickle cell disease (SCD) is an inherited genetic disorder that affects the African American community disproportionately. Research has grown SCD knowledge by leaps and bounds from Dr. James Herrick's description of peculiar shaped red blood cells in 1910 to the innovative CRISPR-cas9 technology. With a multifaceted pathophysiology triggered by a single amino acid substitution, SCD can cause varying degrees of chronic hemolytic anemia, vasculopathy, vaso-occlusive disease, and multiple-organ damage. Ultimately, it can shorten a patient's life span. Patients with SCD experience considerable barriers to therapy. Three key strategies for preventing SCD complications are screening, prevention of infection or vaso-occlusive crisis (VOC), and immunizations. This activity focuses on SCD's complications and the therapeutic agents available to treat SCD.

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## INTRODUCTION

Sickle cell disease (SCD) is an inherited, lifelong blood disorder causing severe complications involving multiple organ systems. SCD affects approximately 100,000 Americans.<sup>1</sup> Disproportionately affecting the Black or African American community, 1 of every 365 Black or African American babies is born with SCD. About 1 in 13 Black or African American babies is born with sickle cell trait, meaning they carry the gene mutation but do not express the disease (see **SIDEBAR**). Physician James Herrick described SCD about 100 years ago after observing a case of severe malaise and anemia in a young dental student from Grenada.<sup>2</sup> Linus Pauling's discovery of the abnormal protein hemoglobin S as the cause of SCD paved the way for treating SCD as a "molecular disease."

**PAUSE AND PONDER:** Why do patients with SCD have high 30-day re-admission rates?

In SCD, a mutation in the beta-hemoglobin gene results in the sickle cell hemoglobin (HbS) synthesis. Different SCD genotypes (genetic characteristics) manifest as different disease phenotypes (physical characteristics), described in **Table 1**. Deoxygenated HbS polymerizes and alters red blood cell (RBC) structure and function. Resulting RBCs are sickle-shaped, less flexible, and highly adhesive compared with normal RBCs. Sickled RBCs cannot easily pass-through blood vessels. RBCs may undergo sickling or unsickling depending on oxygen availability in an organ and its duration of exposure to a deoxygenated environment.<sup>5</sup> A damaged, sickled RBC's life span is roughly one-sixth that of a normal RBC due to repeated cycles of sickling and unsickling. This produces two hallmarks of the disease: blood vessel occlusion and chronic hemolytic anemia.

Clinicians refer to acute sickle cell pain as “vaso-occlusive sickle crisis” or VOC.<sup>5</sup> Patient-related and environmental risk factors may trigger a VOC episode that can last up to a week<sup>4</sup>:

**Patient-related factors:** acidosis, alcohol consumption, anxiety/depression, dehydration, fever, hypoxia, infection, , menstruation, obstructive sleep apnea, pain, physical exhaustion, and pregnancy

**Environmental:** Exposure to high temperature, humidity, and wind speed

**SIDEBAR: Sickle Cell Trait**

Individuals who inherit one sickle cell gene and one normal gene have sickle cell trait (SCT). Experts estimate 8% to 10% of African Americans have SCT.<sup>3</sup> Globally, prevalence as high as 40% has been reported among certain African tribes, Mediterranean populations, and Indian aboriginal groups.<sup>3</sup>

Most people with SCT will have no symptoms or health complications.<sup>3</sup> When patients with SCT are exposed to conditions that favor RBC sickling (e.g., high altitude, severe dehydration, extremely high intensity physical activity), they develop symptoms resembling SCD. Complications include rhabdomyolysis (destruction or degeneration of muscle tissue), reduced blood supply to the spleen, or glaucoma.<sup>3,4</sup>

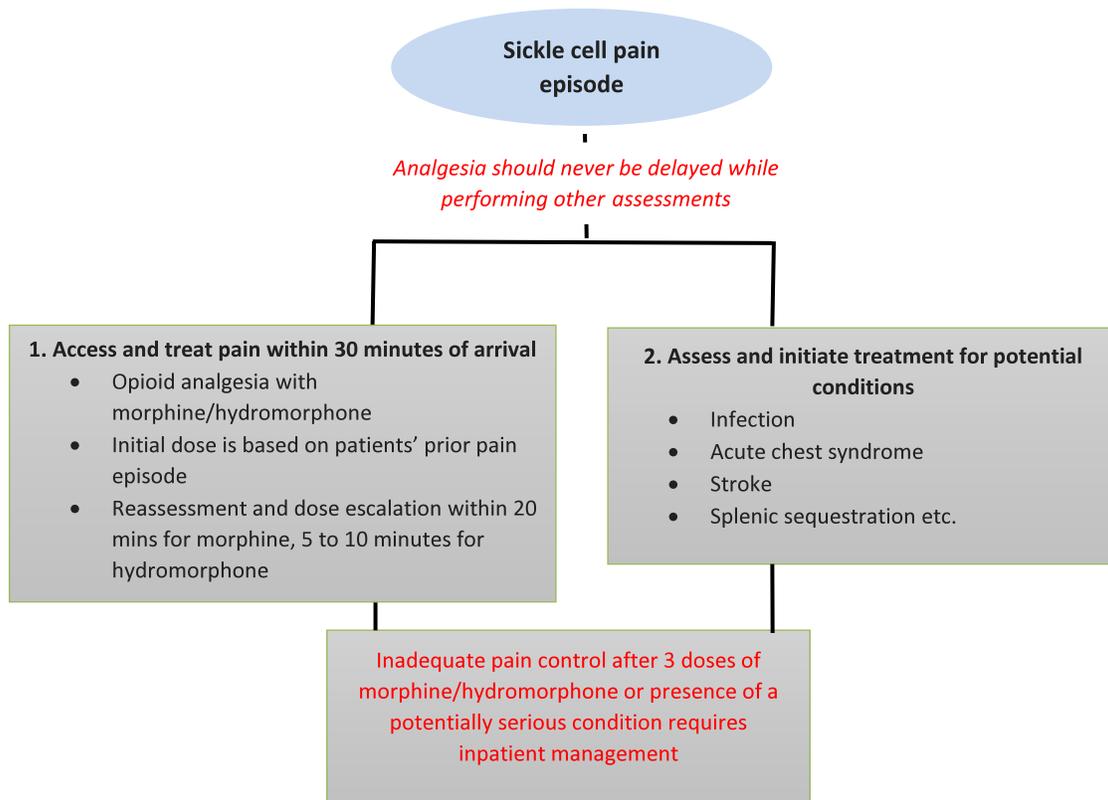
Some controversy exists about testing. Implementation of mandatory testing among athletes has raised controversy due to stigmatization and racial bias concerns.<sup>3</sup> In 2010, the National Collegiate Athletic Association approved mandatory opt-out SCT testing for its Division I athletes following the death of a 19-year-old freshman with undiagnosed SCT. However, in January 2012 the American Society of Hematology released a policy statement on SCT screening and athletic participation that opposed mandatory testing. The statement urged athletic programs to adopt universal preventive interventions, including drinking adequate fluids, taking rest breaks. and having adequate staff present at organized practices.<sup>3</sup>

**Table 1. Types of Sickle Cell Disease<sup>6</sup>**

| Type of Hemoglobin  | Disease Phenotype   |
|---------------------|---|
| HbSS                | The most common and severe form of SCD, referred to as “sickle cell anemia.” Hemolysis and anemia by age 6 to 12 months. Patients inherit two sickle cell genes (S), one from each parent.                      |
| HbSC                | Second most common type of SCD. Patients inherit a sickle cell gene (S) and an abnormal Hb gene (C). Symptoms similar to SCD, but anemia is milder.   |
| HbSbeta-thalassemia | Two forms of beta-thalassemia<br>1. Combination of S with beta plus-thalassemia produces less severe form of SCD<br>2. Combination of S with beta zero-thalassemia produces HbSS phenotype with severe symptoms |
| HbSO                | Patients inherit one sickle cell gene (S) and one abnormal type of hemoglobin O. Less common and symptoms not severe.   |
| HbSE                | Patients inherit one sickle cell gene (S) and one abnormal type of hemoglobin E. Less common and symptoms not severe.   |
| HbSD                | Patients inherit one sickle cell gene (S) and one abnormal type of hemoglobin D. Less common and symptoms not severe.   |
| HbAS                | Patients with one normal gene (A) and one sickle cell gene (S) have sickle cell trait. They usually do not have the signs of the disease but can pass the trait to their biological children.                   |

*Hb, hemoglobin; SCD, sickle cell disease*

*Each hemoglobin molecule has two beta-globulin proteins encoded by two different genes, one inherited from each parent.*



**Figure 1. Overview of pain management for a VOC episode<sup>16</sup>**

Presence of high platelets, neutrophils, hemoglobin (Hb), and unbound extracellular Hb in the blood can also be risk factors for VOC. Recurrent episodic acute clinical events result in acute pain and accumulative organ damage.

### Barriers to Care

Since Pauling’s discovery, researchers have made great strides in understanding SCD’s pathophysiology, but treatment development has been painfully slow. The United States (U.S.) Food and Drug Administration (FDA) approved L-glutamine in 2017 as a new treatment for SCD, the first in almost 20 years. In a cross-sectional study, researchers analyzed disease funding and productivity metrics for SCD and cystic fibrosis (CF) between 2008-2018.<sup>7</sup> Both SCD and CF are inherited diseases with disease exacerbations requiring hospitalization. Both diseases received similar funding despite SCD’s higher prevalence. When the economists factored in disease-specific private foundation funding, the funding disparity was markedly increased.<sup>7</sup>

Patients with SCD have worse health outcomes compared to other diseases and have lower access to care. In 2018, the Centers for Disease Control and Prevention established the Sickle Cell Data Collection (SCDC) program to collect health information about patients with SCD. They hoped to study the long-term trends in diagnosis, treatment, and healthcare access.<sup>8</sup> Currently, 12 states participate in the program. SCDC data can influence policy, healthcare practices, and treatment development, which can improve access and outcomes for patients who have SCD.

SCD is associated with life-threatening complications. Acute pain episodes (or VOC) often result in hospital readmissions, placing enormous financial burden on the healthcare system. Authors of a recent study reported among patients with SCD experiencing an acute pain episode, readmission rates were 7.6% and 26.9% within 7 days and 30 days, respectively.<sup>9</sup> The mean length of hospital stay for readmitted patients was significantly longer than the original hospitalization. In 2016, 30-day readmissions in the U.S. incurred 95,445 extra days of hospitalization, \$152 million in hospitalization costs (expenses incurred by the hospital to provide patient care), and \$609 million in total hospitalization charges (the amount billed to the payer according to the hospital’s price list).<sup>9</sup>

Improvements in treatment and healthcare have afforded most patients with SCD the ability to live into adulthood, but severe SCD can shorten a patient’s lifespan by 20 to 30 years.<sup>10</sup> Poor health outcomes in SCD stem from

- lack of access to quality comprehensive care
- few trained health professionals for SCD
- under-prescribing
- patient misconceptions of the disease
- negative prescriber attitudes towards patient reports of pain

The key to preventing readmissions is a comprehensive healthcare maintenance program. Patients with SCD require an inter-

**PAUSE AND PONDER:** What is the difference between sickle cell trait and SCD? What are the implications for patients and their families?

professional team for disease management, including a general surgeon, hematologist, internist, nurse practitioner, orthopedic surgeon, pharmacist, and pulmonologist.

## SICKLE CELL DISEASE COMPLICATIONS

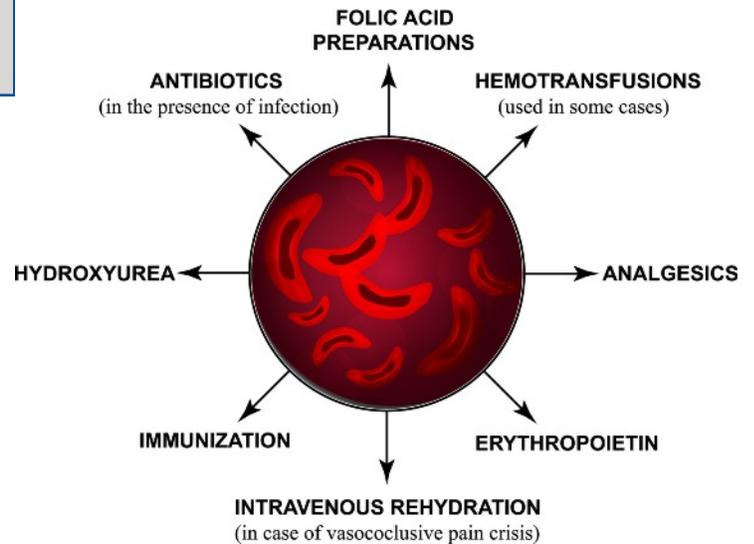
### Acute Pain Episodes

VOC pain episodes are the leading cause of SCD-related hospitalizations.<sup>11</sup> When cell aggregates block blood flow in small vessels, it results in downstream deprivation of nutrients and oxygen ending in tissue ischemia and death. Patients with SCD experience excruciating pain caused by VOC and ischemic tissue damage, and this pain may last hours to days. Acute VOC pain can begin as early as 6 months of age and may be a lifelong condition. The earliest disease manifestation in infants and children is dactylitis (pain or swelling in the hand/feet joints). Pain location varies by age, presenting commonly in the extremities of young children and in the head, chest, abdomen, and back of older individuals.<sup>11</sup>

Opioids constitute the mainstay of treatment in VOC, despite considerable progress made in understanding the disease (see [Figure 1](#), previous page). Healthcare providers harbor several misconceptions about opioid medication use in SCD. The opioid epidemic has increased the barriers to analgesic care in patients with SCD. The U.S. Department of Health and Human Services assembled its Pain Management Best Practices Inter-Agency Task Force in 2016. Following a year-long investigation, their final report identified significant healthcare disparities in the access to and delivery of comprehensive pain care and mental health services in patients with SCD.<sup>12</sup> Stigma, negative provider attitudes and perceived racial bias impede evidence-based care, leading to poor health outcomes. The National Heart, Lung, and Blood Institute (NHLBI) guidelines recommend that providers treating acute SCD pain episodes initiate individualized opioid analgesia within 30 minutes.<sup>13</sup> In 2020, the American Society of Hematology released updated treatment guidelines for acute and chronic pain management in SCD.<sup>14</sup>

Patients with SCD with VOC experience a prodromal phase of one to two days, with pain peaking on Day 3 and lasting until day 6 or 7 before resolving.<sup>4</sup> In addition to acute pain episodes, VOC can lead to acute chest syndrome (described below), hepatic and renal involvement, stroke, and multi-organ failure resulting in death.

## TREATMENT OF SICKLE CELL ANEMIA



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### Acute Chest Syndrome

Acute Chest Syndrome (ACS)—the development of new pulmonary infiltrate accompanied by fever, chest pain, tachypnea (abnormally rapid breathing), wheezing, or cough—is a serious SCD complication. It occurs in about 10% to 20% of hospitalized patients with SCD, and it is associated with high morbidity and mortality rates.<sup>15</sup> ACS develops in the setting of a vaso-occlusive episode or other acute manifestations of SCD one to three days after admission for severe VOC pain. It may progress rapidly to acute respiratory distress syndrome, respiratory failure, pulmonary infarction (blockage of a lung blood vessel by a pulmonary embolus), severe pain, and/or death.<sup>15</sup> Multiple etiologies for ACS are possible, including fat emboli from bone marrow infarcts, pneumonia, pulmonary infarction, and pulmonary emboli. Providers manage ACS acutely with antibiotics, supplemental oxygen, intravenous fluids, and blood transfusions.<sup>15</sup>

### Splenic Sequestration Crisis

Young children between six months and three years of age may experience splenic sequestration following a febrile illness.<sup>17</sup> This occurs in 10% to 30% of young children with SCD.<sup>13</sup> Sickled RBCs are unable to pass through the small endothelial slits of the venous sinuses. Even though these events self-resolve, splenic sequestration can contribute to splenic auto-infarction (tissue death due to oxygen shortage) over time. However, when the mechanical obstruction spreads, the spleen fills with RBCs that cannot exit. As RBCs become trapped in the spleen, Hb levels drop acutely by 2 g/dL and splenomegaly (spleen enlargement) develops. Children present with an abrupt onset of pallor, weakness, and tachycardia. Management of acute splenic sequestration requires RBC transfusion to restore circulating blood volume. The natural history in most children with HbSS or HbS/beta-zero thalassemia is dysfunctional spleen development within the first year of life and splenic auto-infarction by age



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five. Children are also at increased risk of sepsis and infection due to splenic dysfunction.<sup>17</sup>

### Infections

Encapsulated bacteria such as *Streptococcus pneumoniae*, *Neisseria meningitides*, and *Haemophilus influenzae* type b frequently infect children with SCD.<sup>18</sup> The spleen plays a key role in synthesizing antibodies and removing antibody-coated bacteria and antibody-coated RBCs. Functional asplenia (absence of a spleen) resulting from sickling can leave affected children vulnerable to repeat infections. Vaccination programs (i.e., ensuring use of pneumococcal conjugate vaccines) and prophylactic penicillin have drastically reduced pneumococcal disease incidence. Patients with SCD are at increased risk of other infections, including osteomyelitis caused by *Staphylococcus aureus*, *Salmonella* species, or other organisms. *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Streptococcus pneumoniae* are implicated in ACS.<sup>18</sup>

### Stroke

Patients with SCD can also experience neurological complications. These include cerebral blood flow abnormalities, cerebral hemorrhage, microvascular disease, silent cerebral infarcts (SCIs), and stroke.<sup>11</sup> Stroke is a leading cause of disability in SCD. Ischemic stroke (blockage of blood supply to the brain) is more common in children and hemorrhagic stroke (bleeding in/around the brain) is more common in adults. About 11% of children experience overt strokes with peak occurrence between two to nine years of age. Patients may experience recurrent strokes; 50% to 70% of individuals experience another episode within three years after the first event. SCIs are lesions that cause no overt neurological symptoms but identified on imaging studies. SCI lesions may be associated with neurocognitive deficits and they increase the risk for overt stroke.<sup>11</sup>

### Aplastic Crisis

Parvovirus infection in children with SCD can lead to acute, life-threatening anemia temporarily interrupting erythropoiesis.<sup>11</sup>

Sickled RBCs survive for seven to 12 days compared to the 100 to 120 day lifespan of normal RBCs. Parvovirus infection can interrupt erythropoiesis for eight to 10 days resulting in 1 g/dL per day drop in Hb, leading to life-threatening Hb levels. At that point, patients may require RBC transfusion.<sup>11</sup>

### SICKLE CELL DISEASE TREATMENT

Hydroxyurea, RBC transfusions, and opioids are the mainstay of VOC symptom management. Hematopoietic stem cell transplantation and gene therapy are the available curative options. Newer agents include crizanlizumab, L-glutamine, and voxelotor.

SCD is the consequence of a single amino acid substitution—A to T point mutation—in the beta globulin gene. This disease's pathophysiology is a complex network of interdependent processes. Individuals with the HbSS or HbS beta-zero thalassemia have the SCD phenotype. Phenotypic manifestations of SCD may vary in frequency and severity between patients and within the same patient over time. Complications occurring in childhood may disappear or worsen with age. Treatment is based on general management of specific disease complications.

Researchers have pursued multiple therapeutic strategies<sup>19</sup>:

- Targeting HbS polymerization
  - ❑ Blocking intermolecular contacts in the sickle fiber
  - ❑ Inducing fetal hemoglobin (HbF) synthesis
  - ❑ Reducing intracellular HbS concentration
  - ❑ Increasing oxygen affinity
  - ❑ Reducing the concentration of 2,3-diphosphoglycerate to increase Hb's oxygen affinity
- Targeting downstream sequelae of HbS polymerization
  - ❑ Antioxidant therapy
  - ❑ Antiadhesive therapy

**PAUSE AND PONDER:** What does the pharmacy team need to consider when patients with SCD need treatment with medication?

### Therapy's Mainstay: Hydroxyurea

In 1998, the FDA approved hydroxyurea for the treatment of SCD. Hydroxyurea's exact mechanism of action in SCD is still unclear, but researchers have identified a few possibilities.<sup>20</sup> This drug inhibits ribonucleotide reductase, arresting the cells in the S-phase of the cell cycle. This shifts gene expression, resulting in HbF induction. HbF, a form of Hb with higher oxygen affinity, is produced during fetal development and early infancy. Hydroxyurea increases the HbF per erythrocyte, the proportion of HbF-containing cells, and overall percentage of HbF. This increase in HbF relative to HbS results in less polymerization and precipitation of RBCs. Hydroxyurea lowers hemolysis and adhesion and improves blood flow through the microcirculation resulting in fewer vaso-occlusive events. Research has also proposed that hydroxyurea could function through nitric oxide release, leading to vasodilatation and improved vascular response.<sup>20</sup>

### Hydroxyurea in Children

SCD's associated morbidity and organ dysfunction often begin in the first year of life. In December 2017, the FDA approved hydroxyurea use in patients aged two and older with SCD with recurring moderate to severe painful crises.<sup>20</sup> The NHLBI guidelines recommend initiating hydroxyurea in all infants with SCD beginning at nine months of age regardless of clinical severity.<sup>13</sup>

Two randomized controlled trials have shown that hydroxyurea is safe to use in children as young as nine months old.<sup>21,22</sup> Researchers conducted one of these trials in infants between ages nine and 18 months in 13 centers.<sup>21</sup> Participants (n = 96) received liquid hydroxyurea 20 mg/kg per day or placebo (n = 97) for two years. Primary endpoints included splenic function and glomerular filtration rate, both of which can worsen early in SCD. Results from the trial showed no significant differences in the primary endpoint between the treatment and placebo groups. However, treatment group participants reported significant reductions in rates of dactylitis, pain, hospitalizations, and transfusions. The therapy was well tolerated with mild to moderate neutropenia reported as a frequent adverse effect.<sup>21</sup>

Transcranial doppler (TCD) is a noninvasive and painless ultrasound technique to evaluate blood flow. Providers use it to determine a patient's stroke risk. Children with SCD and high TCD flow velocities require regular blood transfusions to prevent primary stroke.<sup>23</sup> The TWITCH trial—a multicenter randomized phase 3 trial—compared hydroxyurea to transfusions for primary stroke prevention and iron overload management. The study enrolled children (N = 121) aged between 4 and 16 years. Participants received standard monthly transfusions (n = 61) or oral hydroxyurea at 20 mg/kg per day (n = 60), which was escalated to the participants' maximum tolerated dose. The primary end-

point was noninferiority for TCD velocity at 24 months, which investigators observed at the first interim analysis, prompting them to terminate the trial early. They concluded that hydroxyurea was a viable alternative to chronic transfusion in select patients for primary stroke prevention.<sup>23</sup>

### Hydroxyurea in Adults

The landmark Multicenter Study of Hydroxyurea in Sickle Cell Anemia was a phase 3 double-blind, randomized controlled trial in patients with severe SCD.<sup>24</sup> This study demonstrated hydroxyurea treatment significantly reduced the time to first painful crisis and reduced frequency of ACS, number of blood transfusions, and hospitalizations. Hydroxyurea use also improved Hb concentration, mean corpuscular volume, HbF levels, white blood cell counts, absolute reticulocyte count, and measures of hemolysis. After 17.5 years of follow up, investigators found that hydroxyurea improved survival without major serious adverse effects.<sup>25</sup> Cumulative event rates did not indicate that hydroxyurea increased serious complications (e.g., infections, neoplastic disease, stroke).<sup>25</sup>

*Dosing and Response.* Hydroxyurea effects are dose dependent. A recent clinical trial showed laboratory and clinical benefits when hydroxyurea is escalated to the maximum tolerated dose (MTD) compared to fixed dose in a limited resource setting.<sup>26</sup> MTD is the stable and tolerated dose (mg/kg/day) that achieves mild marrow suppression determined by both absolute neutrophil count (1.5 to 3.0 x 10<sup>9</sup>) and reticulocyte count (100 to 200 x 10<sup>9</sup>) over 24 consecutive weeks.<sup>20</sup>

Providers initiate hydroxyurea tablets (Siklos) at 20 mg/kg once daily.<sup>27</sup> They can then increase the dose by 5 mg/kg/day every eight weeks (or sooner if VOC occurs) until MTD or 35 mg/kg/day is achieved, and blood counts are acceptable (see [Table 2](#), next page). Clinicians must monitor blood counts every two weeks. If blood counts are in the toxic range, they should discontinue hydroxyurea until hematologic recovery. When blood counts recover, patients may resume treatment at 5 mg/kg/day less than the dose associated with hematologic toxicity. In patients with renal impairment (CrCl < 50 mL/min), prescribers should reduce the hydroxyurea dose by 50%.<sup>27</sup>

Patients on hydroxyurea capsules (Droxia) begin treatment at 15 mg/kg/day as a single dose.<sup>28</sup> If blood counts are in an acceptable range, the dose may be increased by 5 mg/kg/day every 12 weeks to MTD or 35 mg/kg/day. If blood counts are in the toxic range, patients must discontinue the medication. Once the blood counts recover, patients may resume treatment after a dose reduction of 2.5 mg/kg/day from the dose associated with toxicity. Prescribers titrate hydroxyurea capsules up or down every 12 weeks in 2.5 mg/kg/day increments until the patient achieves a stable dose with no toxicity for 24 weeks. If blood counts are between the acceptable and toxic range, then the dose is appropriate and does not need adjustment.<sup>28</sup>

**Table 2. Hydroxyurea Tablet Dosing Based on Blood Count<sup>27</sup>**

| Clinical Situation               | Definition   | Dose   | Modification  |
|----------------------------------|--|--|---|
| Initiation                       | N/A  | 20 mg/kg/day   | (monitor blood counts every 2 weeks)  |
| Blood counts in acceptable range | Neutrophils $\geq$ 2000 cells/mm <sup>3</sup><br>Platelets $\geq$ 80,000 cells/mm <sup>3</sup><br>Hb $\geq$ 5.3 g/dL<br>Reticulocytes $\geq$ 80,000 cells/mm <sup>3</sup> if Hb $<$ 9 g/dL | Increase dose by 5 mg/kg/day every 8 weeks or if VOC episode       | Increase dose if blood counts are acceptable or VOC<br>Do not increase if myelosuppressed                                       |
| Blood counts in toxic range      | Neutrophils $<$ 2000 cells/mm <sup>3</sup><br>Platelets $<$ 80,000 cells/mm <sup>3</sup><br>Hb $<$ 4.5 g/dL<br>Reticulocytes $<$ 80,000 cells/mm <sup>3</sup> if Hb $<$ 9 g/dL             | Discontinue  | Discontinue until blood counts recover  |
| After blood counts recover       |  | Reduce dose by 5 mg/kg/day from last dose associated with toxicity | May titrate dose up or down every 8 weeks in 5 mg/kg/day increments<br>Discontinue treatment if patient develops toxicity twice |

Hb, hemoglobin; VOC, vaso-occlusive crisis

**Adverse Effects.** Hydroxyurea's common adverse effects (>10%) are diarrhea, leukopenia, mouth sores, nail/skin hyperpigmentation, nausea/vomiting, neutropenia, and reticulocytopenia.<sup>20</sup> Rare side effects include allergic reactions, increased alanine aminotransferase (ALT) and/or creatinine, malignancy, and skin ulcers. Advise patients to wear sunscreen and avoid sun exposure. They should also avoid receiving a live vaccine while on hydroxyurea, as administration may result in severe infection and decreased antibody response.<sup>28</sup> Concomitant hydroxyurea use with antiretroviral drugs can cause hepatotoxicity, pancreatitis, and peripheral neuropathy.<sup>20</sup>

### Voxelotor (Oxbryta)

Voxelotor is an oral HbS polymerization inhibitor.<sup>29</sup> It binds to the N-terminus of the alpha subunit of HbS to stabilize the oxygenated Hb state. Voxelotor demonstrates dose-dependent inhibition of HbS polymerization by increasing Hb's affinity for oxygen. Voxelotor inhibits RBC sickling, improves deformity, and reduces whole blood viscosity. The FDA approved voxelotor in 2019 for SCD treatment in adults and pediatric patients 12 years and older.<sup>29</sup>

**Clinical Trial.** The Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) trial—a randomized, double blind, placebo controlled multicenter study—evaluated voxelotor's safety and efficacy.<sup>30</sup> Investigators randomized participants into three groups in a 1:1:1 distribution: voxelotor 1500 mg (n = 90), voxelotor 900 mg (n = 90), or placebo (n = 92). Patients had sickle cell anemia (HbSS or HbS beta-zero thalassemia) and about two-thirds received hydroxyurea at baseline. The primary endpoint was the percentage of participants with a Hb response,

defined as an increase of more than 1 g/dL from baseline at week 24. Secondary endpoints included change in Hb level from baseline to week 24, hemolysis laboratory markers, and annual VOC incidence rate.

At week 24, the Hb response was significantly greater in the 1500 mg voxelotor group than the placebo group. The 1500 mg voxelotor group also had significant reductions in hemolysis laboratory markers (i.e., indirect bilirubin, reticulocyte percentage). VOC incidence did not differ among the three trial groups. Adverse events grade 3 or greater and serious adverse events were similar in treatment and placebo groups. The investigators concluded voxelotor provided a significant and sustained Hb increase and reduced the incidence of anemia and hemolysis in SCD.<sup>30</sup>

**Dosing and Administration.** Voxelotor is available in 500 mg tablets.<sup>29</sup> The recommended dose is 1500 mg orally once daily with or without food. If patients miss a dose, they can continue dosing as usual the day following the missed dose. Healthcare providers should advise patients to swallow the tablets whole, without crushing or chewing them. Patients may use voxelotor concomitantly with hydroxyurea. Patients with severe hepatic impairment (Child Pugh C) should decrease to 1000 mg taken once daily with or without food. Renal function has no clinically significant effect on voxelotor excretion. Researchers have not studied voxelotor in patients with end stage renal disease requiring dialysis.<sup>29</sup>

Strong CYP3A4 inhibitors or inducers mediate voxelotor oxidation.<sup>29</sup> The manufacturer recommends avoiding administration of strong CYP3A4 inhibitors or strong/moderate CYP3A4 inducers with voxelotor. If concomitant administration is unavoidable, patients taking strong CYP3A4 inhibitors or fluconazole should decrease the voxelotor dose to 1000 mg once daily. Those taking strong or moderate CYP3A4 inducers should increase to 2500 mg once daily. The manufacturer recommends avoiding co-administration of voxelotor with CYP3A4 substrates with a narrow therapeutic index.<sup>29</sup>

**Adverse Effects.** In the HOPE trial, 23% of patients in the 1500 mg treatment group developed headache, hypersensitivity reactions, and one patient developed pulmonary embolism.<sup>30</sup> Clinical manifestations of hypersensitivity reactions included generalized rash, urticaria, mild shortness of breath, facial swelling, and eosinophilia. Frequent adverse reactions that required dose modification in the clinical trial included diarrhea, headache, rash, and vomiting.<sup>30</sup>

### L-Glutamine (Endari)

L-glutamine is an oral essential amino acid. L-glutamine's exact mechanism of action in SCD is still not fully understood.<sup>31</sup> Sickled RBCs are more susceptible to oxidative stress damage than normal RBCs. Oxidative stress contributes to chronic hemolysis and VOC associated with SCD. Glutamine is a precursor to nicotinamide adenine dinucleotide (NAD) and improves NAD redox potential. NAD and its reduced form (NADH) play an important role in regulating and preventing oxidative damage in RBCs. Studies have shown that L-glutamine uptake is several times greater in sickled RBCs than normal RBCs, primarily to increase the total intracellular NAD levels.<sup>32</sup> The FDA approved L-glutamine in 2017 to treat SCD in adult and pediatric patients aged five and older.<sup>31</sup>

**Clinical Trial.** A phase 3 multicenter, randomized, placebo-controlled, double blind study evaluated the L-glutamine efficacy.<sup>32</sup> Investigators randomized 230 patients (five to 58 years old) 2:1 to receive L-glutamine (n = 152 patients) or placebo (n = 78). The treatment group received L-glutamine twice daily at 0.3 g/kg per dose and the placebo group received 100% maltodextrin. Patients had sickle cell anemia (HbSS or HbS beta-zero thalassemia) and a history of two or more pain crises during the previous year. About 67% of study participants were receiving hydroxyurea and continued therapy for the 48-week study duration. The treatment group had 34 patients aged five to 12 years and 41 patients aged 13 to 18 years.

The primary endpoint was the number of pain crises throughout the study duration. Secondary endpoints were the number of hospitalizations for SCD-related pain, number of emergency room visits, and changes in Hb from baseline through week 48. At week 48, patients in the treatment group had significantly fewer pain crises and hospitalizations than the placebo group. There were no significant differences in Hb changes between the two groups.<sup>32</sup>

**Dosing and Administration.** L-glutamine is available as an oral powder in 5 gram packets.<sup>31</sup> The recommended dose of L-glutamine is 5 to 15 grams orally twice daily based on body weight<sup>31</sup>:

- Weight <66 lbs, 1 packet per dose and 2 packets per day
- Weight 30-65 lbs, 2 packets per dose and 4 packets per day
- Weight >65 lbs, 3 packets per dose and 6 packets per day

Patients mix each dose of L-glutamine with eight ounces of a cold or room temperature beverage or four to six ounces of food before ingestion. Complete dissolution is not required prior to administration.<sup>31</sup>

**Adverse Effects.** In the phase 3 clinical trial, patients in the treatment group experienced low-grade nausea, noncardiac chest pain, fatigue, and musculoskeletal pain more frequently than the placebo group.<sup>32</sup>

### Crizanlizumab (Adakveo)

Crizanlizumab is an intravenous monoclonal antibody that binds to P-selectin and blocks interactions with its ligands.<sup>33</sup> P-selectin functions as a cell adhesion molecule, which helps cells stick to each other or their surroundings. Binding of P-selectin on the surface of activated endothelium and platelets prevents interactions between endothelial cells, platelets, RBCs, and leukocytes. The FDA approved crizanlizumab in November 2019 to reduce VOC frequency in patients aged 16 years and older with SCD.<sup>33</sup>

**Clinical Trial.** A double blind, randomized, placebo-controlled phase 2 trial (SUSTAIN) assessed crizanlizumab's safety and efficacy in patients with SCD.<sup>34</sup> Researchers randomized eligible patients (HbSS, HbSC, HbS, HbSbeta-zero thalassemia, HbSbeta-positive thalassemia) to receive crizanlizumab 5 mg/kg (n = 66) or 2.5 mg/kg (n = 64) or placebo (n = 62). Providers administered crizanlizumab by infusion on week 0, week 2, and every four weeks thereafter. Among the study participants, 62% used hydroxyurea concomitantly. The primary endpoint was annual rate of SCD-related pain crises. Secondary endpoints were annual rate of days hospitalized, times to first and second crisis, annual rate of uncomplicated crisis, annual ACS rate, and the Brief Pain Inventory questionnaire. The median crisis rate per year was 45.3% lower in the high-dose crizanlizumab group compared to placebo. The median time to first crisis, second crisis, and uncomplicated crisis was also significantly lower in the high-dose crizanlizumab group.<sup>34</sup>

Kutlar et al. conducted a post hoc analysis to study crizanlizumab's effect on pain crises in subgroups of patients with SCD.<sup>35</sup> This analysis showed that more patients in the treatment group (crizanlizumab 5 mg/kg) were event free and treatment significantly increased time to first VOC compared to placebo. A phase 3 clinical trial to assess the efficacy and safety of two doses of crizanlizumab with or without hydroxyurea in patients with SCD and VOC is ongoing.<sup>34</sup>

**Dosing and Administration.** Providers administer crizanlizumab by intravenous infusion at 5 mg/kg over a period of 30 minutes at week 0, week 2, and every four weeks thereafter.<sup>33</sup> When patients miss a dose, the manufacturer recommends administering the dose as soon as possible. If crizanlizumab is administered within 2 weeks after the missed dose, the dosing is continued according to the patient's original schedule. If crizanlizumab is administered more than 2 weeks after the missed dose, the dosing is continued every 4 weeks thereafter. The effect of renal or hepatic impairment on crizanlizumab's pharmacokinetics is unknown.<sup>33</sup>

Patients may take crizanlizumab with or without hydroxyurea. Diluted solution must be administered as soon as possible, as it is stable at room temperature for 4.5 hours and refrigerated for up to 24 hours after dilution.<sup>33</sup>

**Adverse Effects.** Adverse effects that occurred in 10% or more of the SUSTAIN trial treatment group and at least twice as often as in the placebo group were arthralgia, diarrhea, pruritus, vomiting, and chest pain.<sup>34</sup> Infusion-related reactions were observed in two patients treated with crizanlizumab. The healthcare team should monitor patients for signs and symptoms of infusion-related reactions, including chills, dizziness, fatigue, fever, nausea, pruritus, shortness of breath, sweating, urticaria, vomiting, or wheezing. Clinicians must discontinue crizanlizumab infusion for severe reactions and institute appropriate medical care. All therapeutic biological proteins have a potential for immunogenicity.<sup>34</sup>

## INVESTIGATIONAL THERAPIES

### Rivipansel

Rivipansel is a pan-selectin antagonist (i.e., inhibits many selectins) with highest antagonistic activity towards E-selectin.<sup>36</sup> By blocking selectin-mediated cell adhesion in SCD, this agent may inhibit RBC interactions and normalize blood flow, reducing inflammation and VOC. In the phase 2 clinical trial, rivipansel during a VOC episode produced a significant reduction in the mean cumulative intravenous opioid dose compared to placebo. Despite promising phase 2 results, investigators terminated a phase 3 rivipansel trial early. This study did not meet its primary endpoint (time to readiness to discharge) and secondary endpoints (time to discharge, cumulative intravenous opioid use, and time to intravenous opioids discontinuation). A post hoc analysis of the phase 3 clinical trial showed patients treated with rivipansel within 26 hours of pain onset experienced statistically significant improvements in the primary endpoint.<sup>37</sup>

### Niprisan (Nicosan)

Niprisan is an herbal agent that has been used in Nigeria to prevent painful crisis with SCD. It is a dry extract preparation of *Piper guineense* (West African black pepper) seeds, *Eugenia*

*caryophyllum* (a variety of cloves) fruits, *Pterocarpus osun* (a tropical tree) stem, and *Sorghum bicolor* (a millet grain) leaves.<sup>38</sup> Authors of a Cochrane review concluded that while niprisan appeared safe and effective in reducing painful crisis over a six month follow-up period, further clinical trials were warranted.<sup>39</sup> The FDA awarded niprisan orphan drug status in 2003, but its manufacturer filed for bankruptcy in 2008. The drug is still awaiting a commercial supplier.<sup>40</sup>

### SC411

In patients with SCD, blood membranes have low docosahexaenoic acid (DHA). SC411 is a novel DHA ethyl ester oral formulation with a propriety delivery platform to enhance bioavailability.<sup>41</sup> The SC411 trial in children with sickle cell disease (SCOT trial) investigated the effect of three doses of SC411 in 67 children five to 17 years old. Among participants, 67% were also taking hydroxyurea. Children in the treatment group had reduced pain, reduced analgesic use, and reduced absence from school at higher doses of 36 mg/kg and 60 mg/kg compared to placebo. SC411 was well tolerated, but some patients reported nausea and abdominal pain. Further trials are warranted for this drug.<sup>41</sup>

### Gene Therapy and Gene Editing

Nearly 70 years after Linus Pauling's discovery of SCD as a molecular disease, cutting edge genetic therapies could potentially cure SCD. Gene therapy involves inserting a new gene into patient cells, and gene editing involves altering the sequence of an endogenous (naturally-occurring) gene. In 2020, physician researchers used clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 technology in two patients to delete BCL11A, the gene responsible for suppressing HbF production.<sup>42</sup> Thus far, treatment is successful and physicians continue to monitor these patients. This clinical trial is the first published gene editing study to cure a genetically inherited disease. Although bone marrow transplant can cure SCD, most patients do not find a suitable donor.<sup>5</sup>

## PHARMACY TEAM IMPACT ON SICKLE CELL DISEASE

Pharmacists—the most accessible healthcare providers—should be actively involved in clinical management of patients with SCD. Patients with SCD face several barriers to care. Negative perceptions of addiction, racial bias, frequent hospitalizations, clinician, and patient knowledge deficit impede patients' ability to receive appropriate care. Patient education is imperative for disease-specific knowledge, health literacy, and self-management. Patients with SCD need frequent monitoring, immunization assessment, and health maintenance. Due to recent therapeutic developments, patients unable to tolerate hydroxyurea now have options. L-glutamine, voxelotor, and crizanlizumab are all specialty medications, so they require extensive pharmacist counseling. These medications may take weeks to manifest ther-

**Table 3. Antibiotics for *S. pneumoniae* Infection Prophylaxis in Children with SCD<sup>16</sup>**

| Age                 | Prophylactic therapy   |
|---------------------|--|
| 3 months to 3 years | Penicillin VK 125 mg orally twice daily  |
| 3 to 5 years        | Penicillin VK 250 mg orally twice daily  |
| Older than 5 years  | Patients may continue or discontinue treatment based on physician recommendation |

**All healthcare providers should remind parents that fever is a medical emergency regardless of prophylactic therapy.**

apeutic effects, and patients may be discouraged by frequent laboratory monitoring and adverse effects.

Pharmacists must take time to stress the importance of adherence and explain therapy benefits, including reduction in VOC episodes, ACS, hospitalizations, and emergency room visits. Three key strategies for preventing SCD complications are (1) screening, (2) preventing infection or VOC episodes, and (3) immunizing appropriately. Patients should receive the appropriate pneumococcal vaccines and prophylactic antibiotics (see [Table 3](#)) to prevent *S. pneumoniae* infections, which are the most common cause of death in children who have SCD.

Technicians also can help patients who have SCD (see the [SIDEBAR](#)).

### Immunization Schedule

Clinicians should follow the recommended vaccine schedule for patients with SCD.<sup>44</sup> Patients must receive the 23-valent pneumococcal polysaccharide vaccine and an altered schedule for the meningococcal vaccine. Patients 6 months and older should receive an annual influenza vaccine. Michigan provides an excellent summary sheet of necessary vaccines for people who have SCD (see reference 44). In some states, pharmacy technicians can immunize and all technicians can enquire about vaccination status, so they also need to know the vaccination schedule.

[Figure 2](#) describes how pharmacy teams can move their care of patients with SCD from GOOD to BEST!

### CONCLUSION

Patients with SCD have life-threatening complications, such as stroke, ACS, and multi-organ failure from VOC episodes. For nearly 20 years, hydroxyurea was the sole drug therapeutic option. With the FDA approval of four new agents, patients with SCD need multi-disciplinary care for comprehensive disease management. Patients with SCD face tremendous barriers to care compared to other diseases. Pharmacist-led educational interventions can improve widespread treatment disparities, increase patient access earlier in the therapy cycle, decrease cost,

### TECH TALK: Money Matters

The newer agents for SCD—L-glutamine, voxelotor, and crizanlizumab—are specialty medications. L-glutamine and voxelotor cost about \$3,500 and \$10,400, respectively, for a 30-day supply in early 2021.<sup>43</sup> The estimated crizanlizumab cost is \$2,500 per vial and may also be associated with additional administration and facility fees. Most patients will require at least three vials per treatment. Hydroxyurea costs about \$1,200 per year in early 2021. Studies have shown hydroxyurea utilization as low as 30% in eligible patients although its benefits outweigh its potential risks.<sup>20</sup>

Pharmacy teams should appreciate that patients on specialty medications face unique administrative and financial barriers. Benefits investigation for specialty medications is complicated. It involves determining coverage options, co-pay amounts, and patients' total cost of therapy. Often, prior authorizations are needed and sometimes appeals are needed when those authorizations are denied. Patients may abandon therapy because the benefits investigation process is arduous and takes time. Manufacturers offer support programs for qualifying individuals, and pharmacy teams can help locate these programs. Patients may also qualify for medication assistance programs through grant funding or the 340B program.

Patients with SCD require comprehensive care. Outpatient pharmacy technicians are the first point of contact for patients and caregivers. Pharmacy technicians must refer patients with new prescriptions for hydroxyurea to the pharmacist for counseling. Patients with SCD need thorough counseling on adverse effects, drug interactions, vitamin supplementation, and immunization requirements.

Specialty pharmacy liaisons (who are often technicians) can work on benefits investigation for crizanlizumab, L-glutamine, and voxelotor. They can also work with the medication assistance coordinator to secure grants or foundation assistance for eligible patients.



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**Figure 2. Helping Patients with Sickle Cell Disease in Your Pharmacy**

**Best**

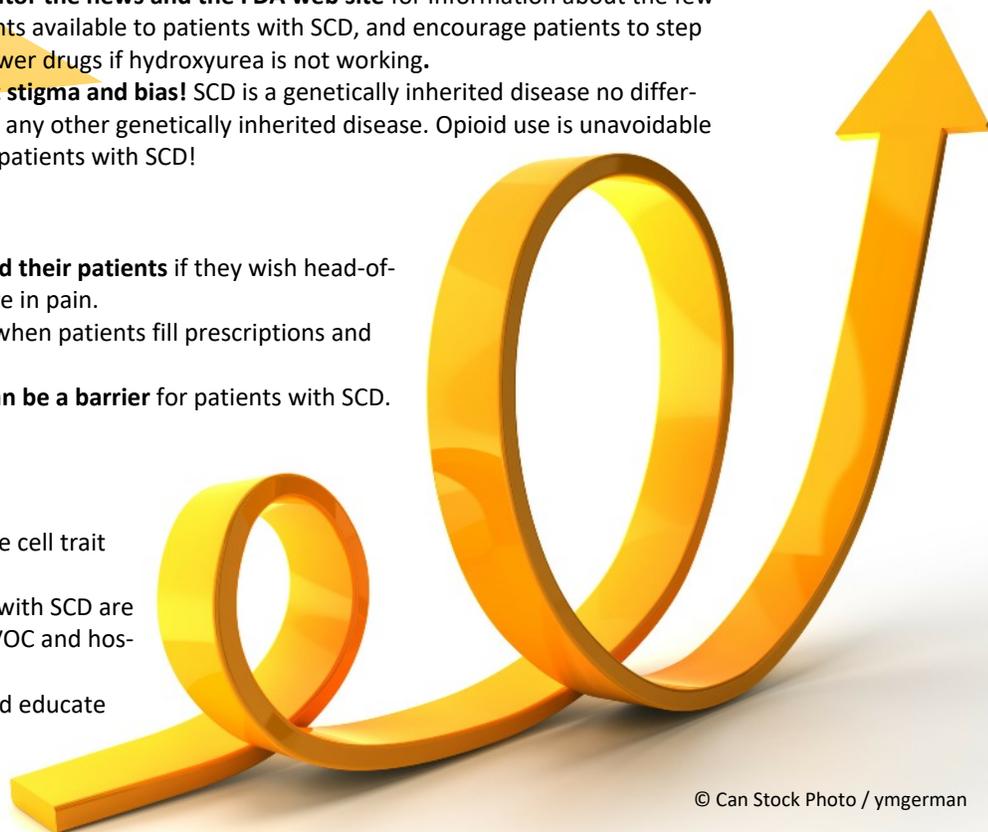
- ① **BE COMMUNITY CHAMPIONS.** Learn your community's cultural composition and volunteer to educate others about this painful disease!
- ② **Monitor the news and the FDA web site** for information about the few treatments available to patients with SCD, and encourage patients to step up to newer drugs if hydroxyurea is not working.
- ③ **Fight stigma and bias!** SCD is a genetically inherited disease no different from any other genetically inherited disease. Opioid use is unavoidable in many patients with SCD!

**Better**

- ① **Always ask patients and their patients** if they wish head-of-the-line privileges if they are in pain.
- ② **Talk about adherence** when patients fill prescriptions and refills for hydroxyurea.
- ③ **Remember that cost can be a barrier** for patients with SCD.

**Good**

- ① **Know the difference** between sickle cell trait and sickle cell disease
- ② **Know which medications** patients with SCD are most likely to use, and which prevent VOC and hospitalization.
- ③ **Identify patients who have SCD** and educate other staff members.



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