Grace Onimoe, MD
Department of Pediatrics, The Metrohealth Hospital, and Assistant Professor, Case Western Reserve University, Cleveland, OH

Seth Rotz, MD
Department of Pediatric Hematology and Oncology and Blood and Marrow Transplant Program, Cleveland Clinic; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Sickle cell disease: A primary care update

ABSTRACT

Sickle cell disease (SCD) is the most common hemoglobinopathy in the United States and causes significant disease-related morbidity including multiorgan damage, chronic anemia, and debilitating pain crises. Primary care physicians play a key role in the medical home model of care for adults with SCD. This review focuses on current recommendations for health maintenance and provides a brief summary of disease complications and current updates.

KEY POINTS

Because SCD is a chronic debilitating condition, there is a need for anticipatory guidance as part of comprehensive care.

Primary care physicians are fundamental to the multidisciplinary approach to improving SCD care.

Disease-modifying therapies, newer hematopoietic stem cell transplant techniques, and gene therapies offer the potential for cure and improved quality of life.

doi:10.3949/ccjm.87a.18051

Approximately 100,000 people live with sickle cell disease (SCD) in the United States, and 1 of every 350 black children is born with the disease.[1] Advances in health maintenance and therapy mean that more young patients are surviving to adulthood, requiring care in the adult primary care setting.

See related editorial, page 28

While the survival rate has improved for adults with SCD, their life expectancy is still more than 2 decades shorter than in the general population, as complications of chronic SCD interact with age-related non-SCD conditions and add to the disease morbidity.[2–5] An alliance of patient, primary care physician, hematologist, and other caregivers is crucial to optimizing disease outcomes, and the primary care physician is an important partner in providing optimal care of these patients.

Here, we review mechanisms of sickle cell disease, common complications and their management based on current guidelines, and current approaches to health maintenance.

UNDERLYING MECHANISMS

The characteristic mutation of SCD at the sixth codon of the beta-globin gene causes a substitution of valine for glutamic acid, resulting in an abnormal hemoglobin tetramer with poor solubility when deoxygenated. The polymerization of deoxygenated hemoglobin S is central to vaso-occlusive phenomena, and this cascades into secondary processes including inflammation, hemolysis, anemia, vasculopathy, and oxidative stress affecting many organs.[1] Other pathways include increased adherence to vascular endothelium, changes in red blood cell membrane structure and func-

TABLE 1

Acute complications of sickle cell disease

Hepatic	Hepatic crisis: right upper quadrant pain, fever, jaundice, nausea, tender hepatomegaly, jaundice
	Hepatic sequestration: abdominal pain, tender hepatomegaly, and acute anemia, but absence of cholestasis or transaminitis
	Acute cholecystitis
Splenic sequestration	Sudden enlargement of spleen due to trapping of the red cell mass
	Presents with left-sided abdominal pain, abdominal distention, pallor, acute anemia, hypovolemic shock
Stroke	Focal seizures, hemiparesis, speech deficits; hemorrhagic stroke more common in adults
Acute ocular conditions	Hyphema, central retinal artery occlusion, orbital infarction, orbital compression syndrome
Acute chest syndrome	Fever, respiratory symptoms, chest pain, new infiltrate on chest radiography, hypoxia, acute anemia
Acute anemia	Decline of the hemoglobin level of 2 g/dL below the baseline value
	Etiology includes red cell aplasia, delayed hemolytic transfusion reaction, acute bleeding (surgery), spleen sequestration
Priapism	Painful sustained penile erection; urinary retention may occur
Fever	Repeated splenic infarctions from vaso-occlusion result in hyposplenism and functional asplenia, leading to increased susceptibility to infection from encapsulated organisms; sickle cell fever, defined as temperature > 38.3°C (101.5°F), should prompt rapid evaluation and initiation of antibiotics
Pain	Acute excruciating pain, most commonly in the extremities, chest, and back; onset may be gradual, duration may be hours to days; triggers include stress, exposure to cold, and infectious illness
Multisystem organ failure	Usually occurs during a vaso-occlusive crisis
	Presents with fever, rapid fall in hematocrit and platelet count, and altered sensorium; respiratory, hepatic, and kidney failure

Data from American Society of Hematology. Management of Acute Complications of Sickle Cell Disease: A Pocket Guide for the Clinician. www.hematology.org/Clinicians/Guidelines-Quality/Quick-Ref/3466.aspx.

Impaired urinary concentrating ability in sickle cell disease can lead to enuresis, polyuria, and dehydration

tion, and ordered cell-volume control.[6]

SCD genotypes common in the United States include SS, SC, sickle–beta zero thalassemia, and sickle–beta plus thalassemia. The most prevalent and severe genotype is homozygosity of the hemoglobin SS mutation, accounting for 60% to 70% of US cases. Sickle cell–beta zero thalassemia (ie, no hemoglobin A production) has a clinical course as severe as homozygous SCD. While other sickle cell variants tend to have a milder clinical course, a broad range of disease severity can be seen within individual genotypes.

GENERAL MANAGEMENT STRATEGIES

Current management strategies include prophylactic penicillin and immunizations to decrease the occurrence of pneumococcal infections, hydroxyurea (a disease-modifying agent), blood transfusions (for symptomatic acute anemia, stroke management, preoperative optimization), and bone marrow transplant. In 2017, the US Food and Drug Administration (FDA) approved L-glutamine oral powder for reducing acute complications of SCD, and many other drugs are in develop-

ment and undergoing clinical testing. Gene therapy is also progressing, with a recently reported successful outcome in 1 patient.[7]

The National Heart, Lung and Blood Institute (NHLBI) has developed guidelines for the care of SCD patients; the most recent version was published in 2014.[8] The American Society of Hematology has developed new guidelines on the management of SCD complications (https://ashpublications.org/bloodadvances/article/3/23/3867/429210/American-Society-of-Hematology-2019-guidelines-for).

ACUTE COMPLICATIONS

Acute complications of SCD (**Table 1**) include hepatic crisis, cholecystitis, splenic sequestration, stroke, acute chest syndrome, acute anemia, priapism, pain, and multisystem organ failure.

CHRONIC COMPLICATIONS

In addition to chronic pain, common complications of SCD include organ damage (kidney, liver, heart, lung), avascular necrosis, cerebral infarction, retinopathy, leg ulcers, and chronic anemia. Though the incidence of these complications increases with older age, onset can occur much earlier.

Kidneys

Chronic kidney disease occurs in 4% to 18%, and early identification is crucial to improved outcomes. Deteriorating renal function contributes to the risk of death after age 40, and progressive glomerular fibrosis is associated with a declining glomerular filtration rate, falling erythropoietin levels, and a gradual decline in total hemoglobin.[9]

Impaired urinary concentrating ability is common in SCD and can lead to enuresis, polyuria, and dehydration.

Liver

Chronic hepatobiliary complications include gallstone disease, viral hepatitis, and cholangiopathy.

Heart and lungs

In adults with SCD, the prevalence of pulmonary hypertension—defined as tricuspid valve regurgitation jet velocity of at least 2.5 m/sec on Doppler echocardiography—has been reported to be as high as 30%.[10] Pulmonary hypertension is often associated with left ventricular diastolic dysfunction. These patients also have a high prevalence of asthma, frequent pain crises, and acute coronary syndrome, and a higher risk of death.[11]

Avascular necrosis

Avascular necrosis resulting from bone necrosis secondary to ischemia affects the femoral and humeral heads most often. Avascular necrosis is typically asymptomatic until late-stage disease, but once it becomes symptomatic, there is a rapid progression to collapse, especially in avascular necrosis secondary to SCD.

Brain

Adults with SCD are prone to new and ongoing silent cerebral infarctions.[12,13] These may lead to decreased intellectual performance and may also become progressive, leading to clinically overt stroke.[12]

Eyes

In SCD, retinopathy triggered by vaso-occlusion of the small vessels of the eye is classified as proliferative or nonproliferative sickle cell retinopathy.[14] Proliferative sickle cell retinopathy is a major contributor to vision loss, leading to visual impairment in 10% to 20% of affected eyes.[15] Sickle cell retinopathy occurs most often in patients with the hemoglobin SC genotype.[15]

Leg ulcers

Leg ulcers occur in 8% to 10% of adults with SCD. The pathogenesis is complex and includes mechanical obstruction by dense red blood cells, venous incompetence, and bacterial infection.[16] Leg ulcers tend to occur in areas with less subcutaneous fat, with thin skin, and with decreased blood flow. The most common site is the lateral malleoli. Less common sites are the anterior tibial area, dorsum of the foot, and Achilles tendon.[16,17]

Thrombosis

SCD is a hypercoagulable state, and various mechanisms are involved, such as enhanced platelet function, activation of the coagulation cascade, and impaired fibrinolysis.[18] Venous thromboembolism affects nearly a quarter of adult patients and appears to be a risk factor for death in SCD.[18–20]

Immunization status should be reviewed to ensure compliance with vaccinations

TABLE 2

Sickle cell disease: Recommended screening and interventions

Nephropathy
Screen annually for albuminuria: spot urine test to estimate protein-to-creatinine ratio
If micro- or macroalbuminuria is present: 24-hour urine test
If protein excretion rate > 300 mg/24 hours, refer to a nephrologist
Consider angiotensin-converting enzyme inhibitor therapy

Pulmonary
Assess for respiratory problems
Pulmonary function testing
If findings suggest pulmonary hypertension, refer for cardiology evaluation

Hypertension
Screen; treat to ≤ 130/80 mm Hg[a]

Retinopathy
Refer to an ophthalmologist for a dilated eye examination[b]; rescreen in 1–2 years if normal
Refer to a retinal specialist for suspected retinopathy

Stroke
Screening limited to children
Blood transfusion: simple or exchange
Hydroxyurea[c]

Leg ulcers
Inspect lower extremities for active and healed ulcers
Treat with debridement, wet-to-dry dressings, topical agents
Chronic recalcitrant deep leg ulcers: evaluate for osteomyelitis, consult wound care specialist

Reproductive counseling
Reproductive life plan
Refer partners for hemoglobinopathy status testing if status is unknown
Test women anticipating pregnancy for red blood cell alloantibodies
Discuss contraception choices with no restrictions for use in sickle cell disease: progestin-only contraceptives, barrier methods; reinforce the need for barrier methods for patients on hydroxyurea

Avascular necrosis
Elicit from history and physical examination
Confirm with radiography and magnetic resonance imaging
Refer for physical therapy, orthopedic clinic

[a] Systolic value based on updated American Society of Hematology guidelines on sickle cell disease management: https://ashpublications.org/bloodadvances/article/3/23/3867/429210/American-Society-of-Hematology-2019-guidelines-for.
[b] Sickle cell retinopathy is more common in the SC variant, but other genotypes carry a risk.
[c] While hydroxyurea has been shown to be comparable to transfusion therapy in the prevention of stroke, chronic transfusions have remained an efficient method of reducing the occurrence of secondary stroke.

From National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: Expert panel report, 2014. www.nhlbi.nih.gov/guidelines.

Enuresis secondary to hyposthenuria can occur, exacerbating dehydration; adult patients may not divulge enuresis voluntarily

Reproductive concerns

Pregnancy in patients with SCD carries serious risks. It is associated with an increased incidence of painful crises, infections, pulmonary complications, thromboembolic events, and antepartum bleeding.[21,22] The risk of maternal death is 6 times higher than in controls, and the risks for preeclampsia, stillbirth, preterm delivery, and infants small for gestational age[21,23] are markedly increased.

Though SCD affects fertility in both males and females, males are more often affected. Fertility problems in men result from erectile dysfunction (from priapism), primary gonadal failure, delayed sexual maturation, and sperm abnormalities.[24,25]

THE MEDICAL HOME MODEL OF CARE

Establishing a medical home—comprehensive care based on a partnership between the patient, family, primary care physician, and other medical staff—is of paramount importance to the care of the SCD patient.

Typically, care is provided by a hematologist in collaboration with the primary care physician. In some instances, a single setting is used, such as a comprehensive sickle cell clinic. Often, a primary care physician knowledgeable in the care of SCD functions as the sole provider. Referral to subspecialists is used as needed to manage disease complications.

Regular medical evaluations

Regular medical evaluations are essential in assessing disease severity and progression. A detailed history and physical examination enable the clinician to note deviations from the previous clinical status and to identify new stressors.

The regular visit is also an opportunity to address chronic complications (**Table 2**), as discussed in the following sections. Efforts should be made to perform a yearly comprehensive review to screen for chronic complications of SCD and to facilitate specialty referrals.

Immunization

Immunization status should be reviewed to ensure compliance with vaccinations (**Table 3**).

Albuminemia

Microalbuminemia screening is done through urinalysis and is confirmed with an albumin-creatinine ratio. For micro- or macroalbuminuria with no other known cause, the NHLBI guidelines recommend angiotensin-converting enzyme (ACE) inhibitor therapy. Since the standard calculations of glomerular filtration rate cannot be used reliably in patients with SCD and in the acute setting, an increase in creatinine of 0.3 mg/dL should prompt an avoidance of nephrotoxic agents.

TABLE 3

Recommended immunizations in sickle cell disease

Vaccine	Recommendation
Haemophilus influenzae	1 dose, if not administered previously
Meningococcal	Meningococcal conjugate vaccine, then a booster every 5 years Serogroup B meningococcal vaccine (2 doses, 2 months apart)
Pneumococcal	PCV 13 (if vaccine-naïve), then PSV 23 8 weeks later Repeat PSV 23 5 years after initial dose
Hepatitis B	3-dose series: 0, 1, and 6 months
Tetanus booster	Every 10 years

PCV 13 = pneumococcal conjugate vaccine; PSV 23 = pneumococcal polysaccharide vaccine

From the US Centers for Disease Control and Prevention. General best practice guidelines for immunizations: Altered immunocompetence. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html.

Enuresis

Enuresis secondary to hyposthenuria (dilute urine) can occur, exacerbating dehydration. Adult patients may not wish to divulge this information voluntarily.

Pulmonary hypertension

Pulmonary hypertension and acute chest syndrome are major causes of death in SCD. Guidelines for screening in SCD patients by the American College of Chest Physicians and the Pulmonary Hypertension Association recommend echocardiography or testing for plasma N-terminal pro-brain natriuretic peptide. However, the frequency of screening has not been established.[26]

Osteopenia

Osteopenia with or without osteoporosis, defined by decreased bone mineral density, has been reported in up to 80% of adults with SCD. Significant vitamin D deficiency was associated with a higher prevalence of fracture history, secondary hyperparathyroidism, and increased bone turnover.[27] Studies have shown the potential benefit of vitamin D in reducing the number of pain days in SCD.[27,28]

Avascular necrosis

Avascular necrosis can reduce the ability to

Early involvement of a physical therapist and orthopedic specialist can improve function and help assess the need for surgical intervention

TABLE 4

Management of pain in sickle cell disease

Acute pain
Parenteral opioids
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Frequent reevaluation for pain relief

Chronic pain
NSAIDs, gabapentin, antidepressants (tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors)
Opioids: for pain not relieved by nonopioids and nonpharmacologic interventions
Refer to mental health professional as needed for depression, anxiety, dependence on pain medication
Nonpharmacologic: cognitive behavioral therapy, massage, meditation, relaxation techniques, transcutaneous electrical nerve stimulation
Collaborate with patient to develop a written individualized treatment plan
Educate patient to increase oral hydration and use stool softeners as needed

From National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: Expert panel report, 2014. www.nhlbi.nih.gov/guidelines.

perform activities of daily living. Though there is no standardized approach to prevention or therapy, early involvement of a physical therapist and orthopedic specialist can improve function and help assess the need for surgical intervention.

Antibiotic prophylaxis

It has been recommended that patients with SCD who have a history of splenectomy or an invasive pneumococcal infection be placed on indefinite prophylaxis with penicillin.[8]

Chronic pain syndrome

Chronic pain syndrome is described as pain that persists for at least 3 months. It is usually described as pain that is deep, nagging, achy, and constant.[29] Neuropathic pain resulting from peripheral or central nervous system dysfunction manifests as allodynia and hyperalgesia.[29]

Opioids are the mainstay of SCD pain management and may be used in conjunction with nonpharmacologic interventions (**Table 4**). Clinicians need to be wary of stigmatizing these patients as drug-seekers, as this can result in delayed treatment and undertreatment. A doctor-patient relationship based on respect and trust will optimize pain management in these patients, and establishing this type of relationship should be a priority, as well as more frequent monitoring of disease status.

While detailed management of chronic pain and pain crises in SCD is beyond the scope of this article, it should be noted that individualized pain management plans crafted with the participation of the patient or caregiver may help facilitate adherence. Concerns about drug-seeking behavior should be addressed after treatment of acute episodes.

Effects of chronic opioid use (tolerance, dependence, and addiction) occur, and the provider may need to involve a pain management expert for collaboration in patient care.

Neurocognitive effects of sickle cell disease

Neurocognitive dysfunction should be assessed with a focused history (memory deficits, work-school challenges, difficulties with medication adherence), followed by neuropsychiatric evaluation as appropriate. Vichinsky et al[30] reported that adult patients with SCD who did not have neurologic symptoms remained at risk for neurocognitive performance deficits; their anemia may induce neurocognitive impairment secondary to cerebral hypoxemia undetected on standard neuroimaging. Early identification of patients with difficulties on specific measures of neurocognitive function may encourage earlier enrollment in cognitive rehabilitation programs.[30]

Reproductive health

The regular evaluation should include discussion of fertility, contraception, erectile dysfunction, and available treatment options

The regular evaluation should include discussion of fertility, contraception, erectile dysfunction, and available treatment options.

Before conception, genetic counseling should be offered to address modes of disease inheritance and transmission, as well as options for preimplantation genetic diagnosis. Pregnancy in SCD patients is a high-risk condition and warrants care from a team of specialists including a perinatologist, adult hematologist, and specialists involved in the management of SCD-related complications.

Medication adherence

Adherence to medications is a major challenge for patients with SCD. It can be improved during clinic visits by reviewing missed doses and providing tools to aid daily compliance, such as smartphone medication apps, pillboxes, and calendar reminders.

Intravenous access

Patients with SCD undergo repeated interventions that require intravenous access (laboratory analysis, fluid resuscitation, transfusions), and over time, peripheral venous access becomes difficult.[31] Central venous access is often required, and it is important to educate the patient about the proper care of these devices and potential complications such as thrombosis and infection.

Psychosocial support

Patients with chronic illness face psychosocial stressors, and access to psychosocial support (psychologist, counselor, social worker) is of paramount importance in sustaining effective health maintenance strategies. Assistance can be provided for acquiring health insurance and transportation, joining support groups, and addressing educational and vocational goals.

DISEASE-MODIFYING THERAPIES

Hydroxyurea

Hydroxyurea, a fetal hemoglobin-modifying agent, has been in use for several decades in SCD but is underused because of patient and caregiver reluctance to provide consent due to misconceptions about drug side effects gleaned from Internet websites.

Current guidelines recommend starting hydroxyurea in adults with SCD in the following situations:

- 3 or more episodes of moderate to severe vaso-occlusive pain in a 12-month period
- Chronic kidney disease in patients already on erythropoietin to improve anemia
- Chronic SCD-associated pain that interferes with activities of daily living or quality of life
- Severe symptomatic chronic anemia
- Severe or recurrent acute chest syndrome.

During the regular evaluation, educating the patient about the benefits of hydroxyurea and the importance of regular monitoring for adverse effects may affect the patient's choice of initiating therapy.

L-glutamine

L-glutamine, the second drug used to reduce acute complications of SCD, was approved by the FDA in 2017 for use in patients over age 5. Results of a phase 3 trial[32] showed that treatment with L-glutamine led to a statistically significant reduction in the frequency of pain crises and rates of hospitalization. L-glutamine is available as an orally reconstituted powder, administered twice daily, with weight-based dosing.

Emerging drug therapies

Studies are under way to target the various mechanisms underlying SCD. One approach to therapy is reduction of reactive oxygen species by blockade of cellular adhesion, inhibition of hemoglobin S polymerization, and reactive oxygen species-reducing antioxidants.[33]

The role of anticoagulants and platelets in SCD is also being studied.[34] Leukocytes, platelets, and multiple proinflammatory pathways contribute to the pathophysiology of SCD. Hence, several approaches are being studied to determine whether downregulation of inflammatory pathways will ameliorate aspects of SCD.[34]

Crizanlizumab, a monoclonal antibody against P-selectin glycoprotein that is expressed on activated endothelial cells and platelets, and which acts to reduce the frequency of vasco-occlusive crises,[35] was granted a breakthrough therapy designation in January 2019 for the prevention of vaso-occlusive crises in patients with SCD. On November 20, 2019, the FDA approved crizanlizumab for use in SCD patients age 16 and older.

In January 2018, the FDA granted a breakthrough therapy designation to the hemoglobin S polymerization inhibitor voxelotor after preliminary clinical evidence indicated the potential for substantial improvement over available therapies.[36] On November 25, 2019, the FDA granted accelerated approval to voxelotor for SCD patients age 12 and older.

Hematopoietic stem cell transplant

The first stem cell transplant for SCD was reported in 1984 in a child who developed acute myeloid leukemia and was cured of both diseases.[37] To date, more than 1,000 stem cell transplants have been performed for patients with SCD, with an estimated 5-year event-free survival of 91.4%, and an overall survival rate of 92.9%.[38] However, these data encompass patients who had a matched sibling donor, and only 18% of patients with SCD have

Psychosocial support (psychologist, counselor, social worker) is paramount to sustaining effective health maintenance strategies

a matched sibling donor.[39]

Trials of matched unrelated donors in SCD have been limited by high rates of graft-vs-host disease.[40] In many cases, families are willing to accept the risk,[41] but the availability of newer disease-modifying agents and techniques has limited the use of matched unrelated donors.

In 2012, Bolaños-Meade et al published data on a cohort of SCD patients who underwent haploidentical stem cell transplant,[42] in which the donor is a "half match" to the patient, ie, a mother, father, child, sibling, or cousin. In haploidentical transplant, post-transplant cyclophosphamide is used to significantly reduce the risk of graft-vs-host disease. Patients undergoing haploidentical transplant were, however, at high risk for graft loss, resulting in recurrence of sickle cell hematopoietic stem cells.

Since this initial cohort study, changes have been made to haploidentical protocols, leading to a decreased rate of graft loss. At present, more than 2 dozen clinical trials of haploidentical and other stem cell transplant techniques in SCD are enrolling patients. However, given the small number of stem cell transplants performed for SCD, the challenge for any study is to accrue a sufficient number of patients for meaningful results.

Gene therapy in SCD

Despite the success of stem cell transplant in SCD, questions remain about donor sources, graft loss, and graft-vs-host disease. SCD is caused by a single base-pair substitution, and gene therapy offers an attractive mechanism to repair the abnormal beta-globin gene product. Hematopoietic stem cells may be mechanically selected using apheresis techniques from patients with SCD, and therapeutic ex vivo gene transfer can occur in the laboratory prior to reinfusion of cells.

In 2017, Ribeil et al reported on a 13-year-old patient who underwent gene therapy.[7] At 15 months after infusion, the patient had no further sickle cell crises, and the level of anti-sickling beta-globin was greater than 50%, indicating a reduction in sickling properties and disease complications.

With this proof-of-concept study published, further protocols (NCT02186418, NCT03282656, NCT02140554, NCT02247843) have opened to explore different methods of gene transfer, and results are anxiously awaited. With the CRISPR/Caspase 9 gene-editing technique, SCD would seem to be an almost ideal candidate for gene editing of hematopoietic stem cells. Various techniques using CRISPR are plausible, and preclinical studies are under way.[43]

TAKE-HOME MESSAGES

- With new advances, health maintenance and curative therapies are available.
- A team approach including the patient, caregivers, primary care physician, and hematologists is crucial to optimizing disease outcomes.
- The primary care physician is an important partner in providing optimal care to adults with SCD.

***Acknowledgment**: We thank Dr. Peter Anderson, Dr. Anne Neff, Dr. Dana Angelini, and the staff of the Cleveland Clinic Taussig Cancer Center and Department of Pediatric Hematology and Oncology for their contributions to the manuscript.*

REFERENCES

1. **Ware RE, de Montalembert M, Tshilolo L, Abboud MR**. Sickle cell disease. Lancet 2017; 390(10091):311–323. doi:10.1016/S0140-6736(17)30193-9
2. **Thein SL, Howard J**. How I treat the older adult with sickle cell disease. Blood 2018; 132(17):1750–1760. doi:10.1182/blood-2018-03-818161
3. **Serjeant GR, Chin N, Asnani MR, et al**. Causes of death and early life determinants of survival in homozygous sickle cell disease: the Jamaican cohort study from birth. PLoS One 2018; 13(3):e0192710. doi:10.1371/journal.pone.0192710
4. **Gardner K, Douiri A, Drasar E, et al**. Survival in adults with sickle cell disease in a high-income setting. Blood 2016; 128(10):1436–1438. doi:10.1182/blood-2016-05-716910
5. **Elmariah H, Garrett ME, De Castro LM, et al**. Factors associated with survival in a contemporary adult sickle cell disease cohort. Am J Hematol 2014; 89(5):530–535. doi:10.1002/ajh.23683
6. **Bunn HF**. Pathogenesis and treatment of sickle cell disease. N Engl J Med 1997; 337(11):762–769. doi:10.1056/NEJM199709113371107
7. **Ribeil JA, Hacein-Bey-Abina S, Payen E, et al**. Gene therapy in a patient with sickle cell disease. N Engl J Med 2017; 376(9):848–855. doi:10.1056/NEJMoa1609677
8. **Yawn BP, Buchanan GR, Afenyi-Annan AN, et al**. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 2014; 312(10):1033–1048. doi:10.1001/jama.2014.10517
9. **Serjeant GR**. The natural history of sickle cell disease. Cold Spring Harb Perspect Med 2013; 3(10):a011783. doi:10.1101/cshperspect.a011783
10. **Parent F, Bachir D, Inamo J, et al**. A hemodynamic study of pulmonary hypertension in sickle cell disease. N Engl J Med 2011; 365(1):44–53. doi:10.1056/NEJMoa1005565
11. **Blake K, Lima J**. Asthma in sickle cell disease: implications for treat-

ment. Anemia 2011; 2011:740235. doi:10.1155/2011/740235
12. **Solomou E, Kraniotis P, Kourakli A, Petsas T**. Extent of silent cerebral infarcts in adult sickle-cell disease patients on magnetic resonance imaging: is there a correlation with the clinical severity of disease? Hematol Rep 2013; 5(1):8–12. doi:10.4081/hr.2013.e3
13. **DeBaun MR, Armstrong FD, McKinstry RC, Ware RE, Vichinsky E, Kirkham FJ**. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. Blood 2012; 119(20):4587–4596. doi:10.1182/blood-2011-02-272682
14. **Menaa F, Khan BA, Uzair B, Menaa A**. Sickle cell retinopathy: improving care with a multidisciplinary approach. J Multidiscip Healthc 2017; 10:335–346. doi:10.2147/JMDH.S90630
15. **de Melo MB**. An eye on sickle cell retinopathy. Rev Bras Hematol Hemoter 2014; 36(5):319–321. doi:10.1016/j.bjhh.2014.07.020
16. **Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK**. Leg ulcers in sickle cell disease. Am J Hematol 2010; 85(10):831–833. doi:10.1002/ajh.21838
17. **Serjeant GR, Serjeant BE, Mohan JS, Clare A**. Leg ulceration in sickle cell disease: medieval medicine in a modern world. Hematol Oncol Clin North Am 2005; 19(5):943–956. doi:10.1016/j.hoc.2005.08.005
18. **Naik RP, Streiff MB, Lanzkron S**. Sickle cell disease and venous thromboembolism: what the anticoagulation expert needs to know. J Thromb Thrombolysis 2013; 35(3):352–358. doi:10.1007/s11239-013-0895-y
19. **Naik RP, Streiff MB, Haywood C Jr, Nelson JA, Lanzkron S**. Venous thromboembolism in adults with sickle cell disease: a serious and under-recognized complication. Am J Med 2013; 126(5):443–449. doi:10.1016/j.amjmed.2012.12.016
20. **Novelli EM, Huynh C, Gladwin MT, Moore CG, Ragni MV**. Pulmonary embolism in sickle cell disease: a case-control study. J Thromb Haemost 2012; 10(5):760–766. doi:10.1111/j.1538-7836.2012.04697.x
21. **de Montalembert M, Deneux-Tharaux C**. Pregnancy in sickle cell disease is at very high risk. Blood 2015; 125(21):3216–3217. doi:10.1182/blood-2015-04-638288
22. **Howard J, Oteng-Ntim E**. The obstetric management of sickle cell disease. Best Pract Res Clin Obstet Gynaecol 2012; 26(1):25–36. doi:10.1016/j.bpobgyn.2011.10.001
23. **Oteng-Ntim E, Meeks D, Seed PT, et al**. Adverse maternal and perinatal outcomes in pregnant women with sickle cell disease: systematic review and meta-analysis. Blood 2015; 125(21):3316–3325. doi:10.1182/blood-2014-11-607317
24. **AlDallal SM, AlDallal NM**. Infertility issues in men with sickle cell disease. Int J Pregn & Chi Birth 2017; 2(3):88–90. doi:10.15406/ipcb.2017.02.00025
25. **Olambiwonnu NO, Penny R, Frasier SD**. Sexual maturation in subjects with sickle cell anemia: studies of serum gonadotropin concentration, height, weight, and skeletal age. J Pediatr 1975; 87(3):459–464. doi:10.1016/s0022-3476(75)80662-7
26. **Willen SM, Gladwin MT**. What is the role of screening for pulmonary hypertension in adults and children with sickle cell disease? Hematology Am Soc Hematol Educ Program 2017; 2017(1):431–434. doi:10.1182/asheducation-2017.1.431
27. **Osunkwo I, Ziegler TR, Alvarez J, et al**. High dose vitamin D therapy for chronic pain in children and adolescents with sickle cell disease: results of a randomized double blind pilot study. Br J Haematol 2012; 159(2):211–215. doi:10.1111/bjh.12019
28. **Boettger PC, Knupp CL, Liles DK, Walker K**. Vitamin D deficiency in adult sickle cell patients. J Natl Med Assoc 2017; 109(1):36–43. doi:10.1016/j.jnma.2016.10.003
29. **Ballas SK**. Update on pain management in sickle cell disease. Hemoglobin 2011; 35(5–6):520–529. doi:10.3109/03630269.2011.610478
30. **Vichinsky EP, Neumayr LD, Gold JI, et al; Neuropsychological Dysfunction and Neuroimaging Adult Sickle Cell Anemia Study Group**. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. JAMA 2010; 303(18):1823–1831. doi:10.1001/jama.2010.562
31. **Shah N, Landi D, Shah R, Rothman J, De Castro LM, Thornburg CD**. Complications of implantable venous access devices in patients with sickle cell disease. Am J Hematol 2012; 87(2):224–226. doi:10.1002/ajh.22230
32. **Niihara Y, Miller ST, Kanter J, et al; Investigators of the Phase 3 Trial of l-Glutamine in Sickle Cell Disease**. A phase 3 trial of l-glutamine in sickle cell disease. N Engl J Med 2018; 379(3):226–235. doi:10.1056/NEJMoa1715971
33. **Jagadeeswaran R, Rivers A**. Evolving treatment paradigms in sickle cell disease. Hematology Am Soc Hematol Educ Program 2017; 2017(1):440–446. doi:10.1182/asheducation-2017.1.440
34. **Telen MJ**. Beyond hydroxyurea: new and old drugs in the pipeline for sickle cell disease. Blood 2016; 127(7):810–819. doi:10.1182/blood-2015-09-618553
35. **Ataga KI, Kutlar A, Kanter J**. Crizanlizumab for the prevention of pain crises in sickle cell disease. N Engl J Med 2017; 376(5): 429–439. doi:10.1056/NEJMoa1611770
36. **Estepp JH**. Voxelotor (GBT440), a first-in-class hemoglobin oxygen-affinity modulator, has promising and reassuring preclinical and clinical data. Am J Hematol 2018; 93(3):326–329. doi:10.1002/ajh.25042
37. **Johnson FL, Look AT, Gockerman J, Ruggiero MR, Dalla-Pozza L, Billings FT 3rd**. Bone-marrow transplantation in a patient with sickle-cell anemia. N Engl J Med 1984; 311(12):780–783. doi:10.1056/NEJM198409203111207
38. **Gluckman E, Cappelli B, Bernaudin F, et al; Eurocord, the Pediatric Working Party of the European Society for Blood and Marrow Transplantation, and the Center for International Blood and Marrow Transplant Research**. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. Blood 2017; 129(11):1548–1556. doi:10.1182/blood-2016-10-745711
39. **Mentzer WC, Heller S, Pearle PR, Hackney E, Vichinsky E**. Availability of related donors for bone marrow transplantation in sickle cell anemia. Am J Pediatr Hematol Oncol 1994; 16(1):27–29. pmid:8311169
40. **Shenoy S, Eapen M, Panepinto JA, et al**. A trial of unrelated donor marrow transplantation for children with severe sickle cell disease. Blood 2016; 128(21):2561–2567. doi:10.1182/blood-2016-05-715870
41. **Kodish E, Lantos J, Stocking C, Singer PA, Siegler M, Johnson FL**. Bone marrow transplantation for sickle cell disease. A study of parents' decisions. N Engl J Med 1991; 325(19):1349–1353. doi:10.1056/NEJM199111073251905
42. **Bolaños-Meade J, Fuchs EJ, Luznik L, et al**. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. Blood 2012; 120(22):4285–4291. doi:10.1182/blood-2012-07-438408
43. **Ye L, Wang J, Tan Y, et al**. Genome editing using CRISPR-Cas9 to create the HPFH genotype in HSPCs: an approach for treating sickle cell disease and beta-thalassemia. Proc Natl Acad Sci USA 2016; 113(38):10661–10665. doi:10.1073/pnas.1612075113

***ADDRESS**: Seth Rotz, MD, Department of Pediatric Hematology and Oncology, R3, Cleveland Clinic Children's Outpatient Center, 8950 Euclid Avenue, Cleveland, OH 44195; rotzs@ccf.org*
Grace Onimoe, MD, gonimoe@metrohealth.org