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Sickle Cell Disease
A Review

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IMPORTANCE Sickle cell disease (SCD) is an inherited disorder of hemoglobin, characterized by formation of long chains of hemoglobin when deoxygenated within capillary beds, resulting in sickle-shaped red blood cells, progressive multiorgan damage, and increased mortality. An estimated 300 000 infants are born annually worldwide with SCD. Most individuals with SCD live in sub-Saharan Africa, India, the Mediterranean, and Middle East; approximately 100 000 individuals with SCD live in the US.

OBSERVATIONS SCD is diagnosed through newborn screening programs, where available, or when patients present with unexplained severe atraumatic pain or normocytic anemia. In SCD, sickling and hemolysis of red blood cells result in vaso-occlusion with associated ischemia. SCD is characterized by repeated episodes of severe acute pain and acute chest syndrome, and by other complications including stroke, chronic pain, nephropathy, retinopathy, avascular necrosis, priapism, and leg ulcers. In the US, nearly all children with SCD survive to adulthood, but average life expectancy remains 20 years less than the general population, with higher mortality as individuals transition from pediatric to adult-focused health care systems. Until 2017, hydroxyurea, which increases fetal hemoglobin and reduces red blood cell sickling, was the only disease-modifying therapy available for SCD and remains first-line therapy for most individuals with SCD. Three additional therapies, L-glutamine, crizanlizumab, and voxelotor, have been approved as adjunctive or second-line agents. In clinical trials, L-glutamine reduced hospitalization rates by 33% and mean length of stay from 11 to 7 days compared with placebo. Crizanlizumab reduced pain crises from 2.98 to 1.63 per year compared with placebo. Voxelotor increased hemoglobin by at least 1 g/dL, significantly more than placebo (51% vs 7%). Hematopoietic stem cell transplant is the only curative therapy, but it is limited by donor availability, with best results seen in children with a matched sibling donor. While SCD is characterized by acute and chronic pain, patients are not more likely to develop addiction to pain medications than the general population.

CONCLUSIONS AND RELEVANCE In the US, approximately 100 000 people have SCD, which is characterized by hemolytic anemia, acute and chronic pain, acute chest syndrome; increased incidence of stroke, nephropathy, and retinopathy; and a life span that is 20 years shorter than the general population. While hydroxyurea is first-line therapy for SCD, L-glutamine, crizanlizumab, and voxelotor have been approved in the US since 2017 as adjunctive or second-line treatments, and hematopoietic stem cell transplant with a matched sibling donor is now standard care for severe disease.

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Multimedia

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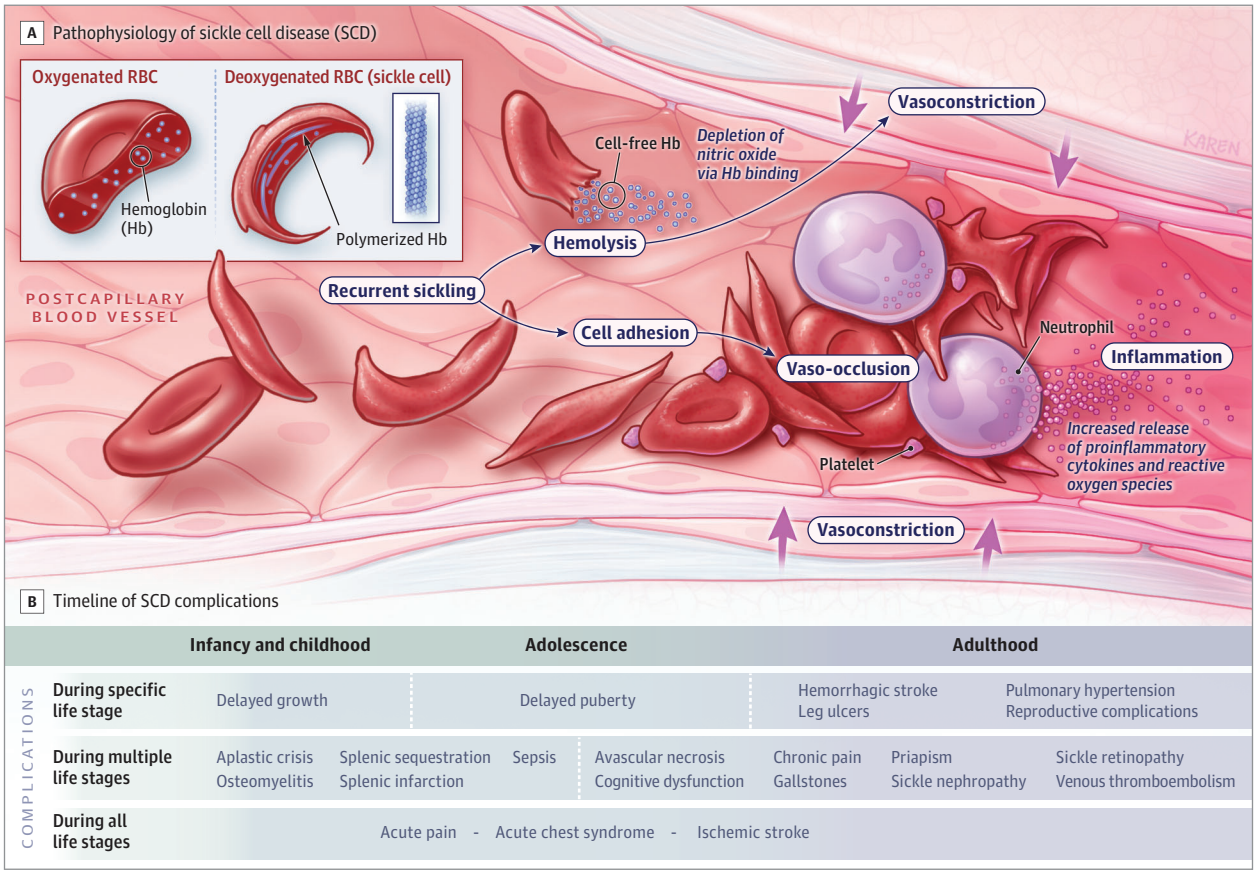
Sickle cell disease (SCD) is a single-gene disorder in which 1 DNA base-pair alteration in the gene coding for hemoglobin produces sickle hemoglobin (HbS) when inherited in an autosomal recessive fashion with a second HbS or when combined with other hemoglobin variants (eg, HbC or β-thalassemia).[1] SCD is associated with damage in multiple organs, including the lungs, kidneys, and the retina, and average life expectancy 20 years less than the general population. Approximately 300 000 infants are born annually worldwide with the severe homozygous form (HbSS disease), with more than half occurring in Nigeria, India, and Democratic Republic of Congo.[2,3] SCD is also common in the Mediterranean region and Middle East and is now present in most countries due to migration and the trans-Atlantic slave trade.[3] In the US, approximately 100 000 people have SCD.[4]

Methods

We searched PubMed for English-language studies of the epidemiology, pathophysiology, diagnosis, treatment, and prognosis of SCD that were published from January 1, 2000, to May 1, 2022, and manually inspected the reference lists of selected articles for other relevant sources. Randomized clinical trials (RCTs), meta-analyses, observational studies, and reviews applicable to a general medical

Figure 1. Pathophysiology and Complications of Sickle Cell Disease (SCD)



A, HbS polymerizes when deoxygenated, inducing recurrent red blood cell (RBC) sickling and hemolysis. The sickled RBCs interact with white blood cells and platelets on vascular endothelium via adhesion molecules which leads to vaso-occlusion. The free Hb and heme released from RBC hemolysis trigger endothelial dysfunction due to depletion of nitric oxide and resultant vasoconstriction. The dual processes of vaso-occlusion and endothelial dysfunction activate inflammatory responses, via increased cytokines and reactive oxygen species, which perpetuates further vaso-occlusion.

B, The morbidity of SCD is progressive throughout the life span. Early on, most complications occur in acute recurrent episodes. Additionally, growth and puberty are delayed due to the increased metabolic demands secondary to ongoing hemolytic anemia. In adulthood, organ damage is prominent in addition to acute complications. Acute pain episodes, acute chest syndrome, and ischemic stroke can occur at any life stage.

readership were prioritized. Of the 3700 papers identified, 115 were selected, including 16 clinical trials, 4 systematic reviews with meta-analyses, 9 systematic reviews without meta-analyses, 33 cohort studies, 14 cross-sectional studies, 4 case series, 24 reviews, and 11 guidelines, scientific statements, or consensus documents.

Pathophysiology

HbS pathology is characterized by polymerization (formation of long chains) of hemoglobin when deoxygenated within capillary beds, which distorts the red blood cell (RBC) into the eponymous sickle shape (**Figure 1**A).[5] Sickled cells differ from normal RBCs because they have increased adhesion molecules that facilitate binding to endothelial walls. Sickled cells hemolyze rapidly, leading to compensatory increases in reticulocyte (immature RBC) production and causing local endothelial dysfunction.[6] The sickling and hemolytic characteristics of sickle RBCs incite an inflammatory cascade through interactions with the endothelium, white blood cells, and platelets.[5] Recurrent RBC sickling and hemolysis, combined with endovascular inflammation, result in acute and chronic organ damage at the cellular level, associated with acute, unpredictable, and potentially life-threatening complications (Figure 1B).[2] Vaso-occlusion, with associated ischemia, is primarily responsible for acute pain, acute chest syndrome (ACS), and avascular necrosis, while hemolysis-related endothelial dysfunction underlies stroke, pulmonary hypertension, priapism, and leg ulcers.[7] Regardless of genotype, clinical severity varies among individuals with SCD, although people who have a heterozygote genotype (eg, HbSC disease) tend to have complications such as splenic infarction and acute pain episodes later in life than people who have a homozygote genotype, who often experience these complications as young children.[8] Additional factors associated with frequency and severity of complications include coinheritance of other globin genetic variants such as α-thalassemia trait and fetal hemoglobin expression.[5]

Diagnosis

Children born in countries with newborn screening programs may be diagnosed shortly after birth. High-performance liquid chromatography or isoelectric focusing tests use dried blood spot samples

Table 1. Therapies for Sickle Cell Disease

	Mechanism of action	Population	Dosing	Main treatment effect	Common adverse effects
Hydroxyurea[29-31]	Increase fetal hemoglobin Reduction in red cell adhesion Reduction in white blood cells and platelets	Individuals with HbSS or HbSβ^0-thalassemia aged ≥9 mo	Initial: 20 mg/kg daily Maintenance: 20-35 mg/kg, maximum dose, 2500 mg daily	Patients (hydroxyurea, n=152 adults; placebo, n=147 adults) had a decrease in painful events from 4.5 to 2.5/y (including acute chest syndrome)[a]	Abdominal pain, nausea, diarrhea Myelosuppression
L-glutamine[27,32]	Increase NADPH and reduce reactive oxygen species	Individuals with SCD aged ≥5 y	For patient weight <30 kg: 5 g twice daily For 30-65 kg: 10 g twice daily For >65 kg: 15 g twice daily	Patients (L-glutamine, n=152; placebo, n=78) had a 25% reduction in VOE 33% Reduction in hospitalization	Flatulence, constipation, nausea, abdominal pain in 20%
Crizanlizumab[25,26]	Anti-P-selectin monoclonal antibody with reduction in red cell adhesion	Individuals with SCD aged ≥16 y	Loading: 5 mg/kg administered intravenously every 2 weeks for 2 doses Maintenance: 5 mg/kg administered intravenously every 4 weeks	Patients (crizanlizumab, n=67; placebo, n=65) had a reduction in VOE from 2.98 to 1.63/y	Infusion-related reactions (nausea, abdominal pain, arthralgia) in 10%-20%
Voxelotor[28]	Increase HbS oxygen affinity with reduced hemolysis	Individuals with SCD aged ≥4 y	For patient weight <40 kg: 600-900 mg once daily For ≥40 kg: 1500 mg once daily	Patients (voxelotor, n=90; placebo, n=92) 51% had an increase in Hb ≥1 g/dL at 24 weeks	Skin rash (15%) Abdominal pain, nausea, diarrhea (20%) Headache (30%)
Allogeneic hematopoietic stem cell transplant[17]	Replace hematopoietic stem cells	Individuals with a matched sibling donor for HbSS or HbSβ^0-thalassemia with severe disease or at high risk		25 Patients normalization of blood counts and elimination of acute SCD events (including pain crises) in 93% (n=25 had reduction of pain crises)	Short-term: transplant-related morbidity (infection, mucositis, pulmonary) Chronic graft-vs-host disease
Gene-directed therapy[33-35]	Express nonsickle hemoglobin Increase fetal hemoglobin Gene correction	Not established (not approved by the US Food and Drug Administration)		Improvement in anemia to near normal Elimination of severe pain crises Possible improvement in quality of life	Short-term: transplant-related morbidity Long-term: adverse events unknown

Abbreviations: Hb, hemoglobin; NADPH, reduced nicotinamide adenine dinucleotide phosphate; SCD, sickle cell disease; VOE, vaso-occlusive episodes.

[a] Cited references for hydroxyurea include adults and children.

from heel sticks to detect the presence of hemoglobin variants (eg, HbS, HbC, and β-thalassemia)[9]; the diagnosis is confirmed by hemoglobin electrophoresis. Although some countries, including the US, perform newborn screening of all infants, in other countries, screening is optional or performed selectively, potentially resulting in failure to diagnose SCD in some patients.[2] These methods are time-consuming, require sophisticated machinery and/or extensive staff training, and require a subsequent visit to convey results[10]; therefore, some confirmed SCD diagnoses may not be communicated to parents. Solubility testing qualitatively screens a capillary blood sample for the presence of HbS in individuals as young as 6 months of age; however, it cannot differentiate between SCD or sickle cell trait and may give false-negative results in patients with the α-thalassemia trait and severe anemia and false-positive results in those with high serum viscosity, erythrocytosis, and leukocytosis.[11] Emerging point-of-care tests may overcome these limitations because they are easy to use, inexpensive, rapid, and accurate.[12] Systematic methods are needed to ensure universal communication of results to families and assistance with follow-up care for people with SCD, especially in communities at risk for loss to follow-up. When SCD is not identified through screening, it may be diagnosed as part of evaluating a normocytic anemia in clinic, evaluating severe atraumatic pain in the emergency department, or in prenatal testing. The number of SCD diagnoses made using each of these methods is unknown.

Management of SCD

With some exceptions, such as sepsis and stroke prevention[13,14] in children, preoperative transfusions,[15] and hydroxyurea therapy,[16] much of the evidence for managing SCD comes from observational cohorts, small RCTs, extrapolation from other populations, and expert opinion.[17-22] Lack of research funding likely contributes to this paucity of high-quality evidence. In 2020, researchers reported that US research funding for cystic fibrosis (US prevalence ≈30 000) was 10-fold greater than for SCD (US prevalence ≈100 000),[23] consistent with findings 14 years earlier.[24]

Medication Therapies for SCD

For nearly 20 years, hydroxyurea was the only therapy approved by the US Food and Drug Administration for adults and children with SCD.[2] Three new drugs for SCD—crizanlizumab,[25,26] L-glutamine,[27] and voxelotor[28]—were approved in the US since 2017 (**Table 1**). Hematopoietic stem cell transplant with a matched sibling donor is now standard care for severe disease,[17] and multiple gene therapy trials are under way.[34] However, these therapies may not be available or affordable for all living with SCD, especially in sub-Saharan Africa and India, where SCD is most common.[3]

Hydroxyurea is a ribonucleotide reductase inhibitor that induces fetal hemoglobin (HbF) production, which is normally

suppressed shortly after birth.[36] In SCD, HbF inhibits HbS polymerization, reducing red cell rigidity and hemolysis, thereby improving anemia. Hydroxyurea also increases nitric oxide (a potent vasodilator), decreases red cell adhesion, and decreases leukocytes (which contribute to vaso-occlusion). Hydroxyurea is first-line therapy for all individuals with HbSS and HbSβ^0-thalassemia and should be prescribed beginning at 9 months of age, based on RCTs that demonstrated decreased incidence of acute pain episodes and ACS with hydroxyurea (Table 1).[29-31] Hydroxyurea should be considered for individuals with other genotypes, such as HbSC and HbSβ$^+$-thalassemia, who have recurrent acute pain episodes, ACS, or hospitalizations.[36] However, recent studies reported that only approximately 28% of eligible children were prescribed hydroxyurea,[37] and only approximately 23% of adults with more than 3 pain crises per year filled a prescription for hydroxyurea.[38] Factors associated with low usage include lack of clinician expertise in SCD and mistrust from a patient population that has been historically underserved, discriminated against, and marginalized.[39,40] Increasing hydroxyurea use in patients with SCD and related diseases should be a top priority.

L-glutamine is an oral amino acid supplement with properties that decrease reactive oxygen species in RBCs, thereby reducing sickling and RBC adhesivity.[32] In an RCT of 230 patients aged 5 years and older, compared with placebo, L-glutamine reduced acute pain crises by 25%, hospitalization by 33%, and mean length of hospital stay from 11 to 7 days. Compared with placebo, L-glutamine reduced ACS (23% vs 9%) and should be prescribed for patients with at least 2 pain crises per year despite hydroxyurea, and those unable to take hydroxyurea.[27]

Crizanlizumab is a monoclonal antibody directed against P-selectin, an adhesion molecule found on activated platelets and endothelial cells that may partially mediate vaso-occlusion. Approval was based on a phase 2 trial of 198 patients aged 16 to 65 years with SCD who were randomized to receive monthly infusion with high-dose crizanlizumab, low-dose crizanlizumab, or placebo.[25] Compared with placebo, high-dose crizanlizumab reduced pain crises from 2.98 to 1.63 per year, and low-dose crizanlizumab reduced pain crises to 2.01 per year. High-dose crizanlizumab (5 mg/kg) is appropriate to prescribe for patients with more than 2 pain crises per year despite hydroxyurea use or for individuals who are unable to take hydroxyurea, similar to those enrolled in the trial.

Voxelotor stabilizes the oxygenated state of Hb in SCD by promoting HbS binding to oxygen, thereby decreasing sickle Hb polymerization and related hemolysis. In an RCT of 198 patients aged 12 to 65 years with severe or symptomatic anemia, voxelotor increased Hb by at least 1.0 g/dL (51%) vs 7% among patients randomized to receive placebo.[28] The effects of voxelotor on clinical outcomes such as pain crises or quality of life are currently unknown. Voxelotor is appropriate for use in patients with low hemoglobin level (trial patients had hemoglobin between 5.5 and 10.5 g/dL) and more than 1 pain crisis per year despite hydroxyurea therapy or for patients unable to take hydroxyurea.

Experimental Therapies

Gene therapy strategies include inserting a gene for a manufactured hemoglobin with antisickling properties via lentiviral vector. One strategy uses HbAT87Q (a manufactured hemoglobin), which is injected into the patient's hematopoietic stem cells and infused back into the patient after a course of chemotherapy. In a case series of 35 patients with HbSS disease infused with HbAT87Q and followed-up for a median of 17.3 months, modified autologous stem cell engraftment occurred in all 35 patients. HbAT87Q comprised at least 40% of total Hb with a concomitant decrease in HbS to 50%, resulting in a significant Hb increase from 8.5 g/dL to 11 g/L and reduced rates of severe pain crises from a median of 3.5 to 0 episodes in a subset of 25 patients who had at least 4 vaso-occlusive events within 2 years of study enrollment.[33] Unexplained anemia with dysplastic features developed in 2 patients, but results of extensive investigation showed that these changes were not consistent with myelodysplasia.

Another strategy of gene therapy is to increase HbF production by decreasing expression of BCL11A, a suppressor of the γ-globin gene that encodes HbF. In a study of 6 patients treated with this strategy, all had HbF expression of 20% to 42% at median 18-month follow-up with no pain crises.[35] Other gene modification targets, such as CRISPR/Cas9 gene correction[41] and other potential disease-modifying therapies, including small molecule pyruvate kinase activators,[42] proinflammatory cytokine inhibitors,[43] and other blockers of cellular adhesion,[44] are in development.

Management of Acute SCD-Related Complications

Acute Pain Episodes (Pain Crises)

Acute pain episodes, also known as pain crises, are the most common complication of SCD and consist of severe, unrelenting, bone pain.[18] The pathophysiology of pain in SCD is complex and involves neuropathic and central pain pathways in addition to local nociceptive pain due to ischemia-reperfusion injury and inflammation.[45] Pain episodes are often preceded by a 1- to 2-day prodromal phase, consisting of fatigue and diffuse body aches that may become more localized, with peak intensity occurring on days 3 to 7 before resolving after several more days.[46] There are no objective signs or laboratory values that can diagnose acute pain crises caused by SCD; patient report is the criterion standard.[46] Therefore, assessing patients for other potential SCD-related complications, such as infectious osteomyelitis or multiorgan failure is important.[31] Patient report of whether the location, intensity, and duration of symptoms are typical of their pain crises should be used to consider whether an alternative diagnosis is likely.

Severe pain episodes often require care in the emergency department for administration of analgesia, usually parenteral opioids (eg, morphine or hydromorphone), with or without nonsteroidal anti-inflammatory agents such as ibuprofen or ketorolac.[18,31] Current guidelines recommend a standardized approach to manage acute pain crises, including rapid triage and timely clinical assessment. The first dose of parenteral opioid analgesia should be administered within 1 hour of arrival to the emergency department. Pain should be frequently reassessed and opioids readministered to attain pain relief.[18,31] A pilot RCT compared an individualized opioid administration strategy, based on daily opioid intake and/or previously effective doses, with a weight-based dosing strategy in 106 adults with SCD and 1 or more prior emergency department visits for pain crisis. Of

patients who received individualized dosing, 40.3% were admitted as inpatients vs 57.5% who received weight-based dosing.[47] A multicenter RCT evaluated 1441 visits for acute pain crises and compared treatment in an infusion center to treatment in the emergency department. Infusion centers had faster initiation of parenteral opioids (62 minutes vs 132 minutes) and lower rates of hospital admission (9% vs 37%).[48] Supplemental oxygen and RBC transfusions are not recommended for routine management of pain crises, and no RCTs have demonstrated that the type of intravenous fluid affects pain intensity or duration. Therefore, treatment with these interventions should be based on clinical assessment and volume status (**Box**).[18] Recent guidelines recommend integrative therapies such as massage and virtual reality; and in the inpatient setting, subanesthetic ketamine and regional anesthesia may be considered for opioid-refractory pain.[18] Of note, the American Society of Hematology endorses the Society of Hospital Medicine's recommendation to avoid daily laboratory evaluations in the setting of clinical stability since phlebotomy can contribute to anemia.[49]

ACS

ACS is defined as a new infiltrate on chest imaging plus any 2 of the following: pleuritic chest pain, hypoxemia, tachypnea, or fever.[50] Children may present with ACS due to infection (ie, pneumonia), or ACS may develop during the first 3 to 4 days of an acute pain episode due to fat embolism, in situ sickling, or thromboembolism.[51] Therapy consists of decreasing the proportion of HbS in circulation via simple transfusion (infusion of packed RBCs) or exchange transfusion (removal of RBCs via erythrocytapheresis or manual phlebotomy plus concurrent infusion of packed RBCs)[20] plus anticoagulation in those with coincident thromboembolism.[21] ACS can be difficult to distinguish from pneumonia. Therefore, antibiotics are usually prescribed, particularly in patients with fever. Rarely, ACS progresses to multiorgan failure syndrome with worsening kidney, hepatic, or neurologic function in addition to respiratory failure.[52]

Fever

Fever in children with SCD can signal sepsis and impeding mortality. Patients with SCD have functional asplenia that predisposes them to infection, especially with encapsulated or atypical bacteria such as *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae*. Prior to the use of penicillin prophylaxis and vaccines for *S pneumoniae* and *H influenzae* in the US (**Table 2**), infection accounted for approximately 50% of deaths in young children with SCD.[54] Fever still requires rapid assessment with complete blood count, reticulocyte count, blood culture, and empirical administration of broad-spectrum antibiotics as adherence rates to penicillin prophylaxis are low,[55] and risk of invasive disease with nonvaccine bacterial serotypes remains high.[56] Adherence to childhood and adult vaccinations schedules for asplenic patients is an important part of health maintenance for individuals with SCD.

Stroke

SCD is the leading cause of ischemic stroke in children.[57] Stroke occurred in approximately 10% of children with HbSS and HbSβ^0-thalassemia before routine screening for abnormal cerebral blood flow velocity with transcranial Doppler ultrasound.[58] US hospital discharge data and SCD prevalence estimates showed the mean annual incidence rate of hospitalization for stroke decreased by 45% from 0.51 per 100 patient-years in 1993-1998 to 0.28 per 100 patient-years in 1999-2009.[59] Acute ischemic stroke in children is usually due to sickle cell–related vasculopathy viewed on imaging as stenosis or complete occlusion of major cerebral arteries with or without development of moyamoya (collateral vessels that appear as "puff of smoke"), and it is treated with emergency RBC exchange transfusion in which the HbS is reduced to less than 30% or HbA greater than 70% for compound heterozygotes (eg, HbSC disease).[22] Adult patients should receive standard therapy for acute stroke, with consideration for thrombolytic therapy and thrombectomy if indicated, followed by RBC exchange transfusion. In adults with SCD and stroke who do not have evidence of sickle cell–related vasculopathy, other causes (eg, patent foramen ovale or antiphospholipid syndrome) should be explored. Risk of ischemic stroke recurrence is decreased through monthly chronic RBC transfusions for children with a goal of maintaining HbS less than

Box. Commonly Asked Questions About Sickle Cell Disease

How Common Is Sickle Cell Disease?

Approximately 300 000 infants are born with sickle cell disease (SCD) each year worldwide. More than half of individuals with SCD globally live in sub-Saharan Africa and India, but it is also commonly seen in the Middle East and Mediterranean. The trans-Atlantic slave trade and immigration introduced SCD to the Americas and Europe. Approximately 100 000 people with SCD live in the US.

How Is SCD Diagnosed?

SCD is a single gene variant in which 1 DNA base-pair alteration in the gene coding for hemoglobin produces sickle hemoglobin (HbS). Countries with newborn screening programs assess infants for SCD shortly after birth and confirm the diagnosis with hemoglobin electrophoresis. Emerging point-of-care tests have advantages over traditional methods for diagnosis because point-of-care tests are easy to use, inexpensive, rapid, and accurate. Systematic methods are needed to ensure universal communication of results to families and assistance with follow-up care for people with SCD, especially in high-risk communities.

How Are SCD-Related Pain Crises Diagnosed and Managed?

Patient report of pain is criterion standard for diagnosing an SCD-related pain crisis; vital sign changes or laboratory values should not be used to confirm or rule out a pain crisis. Severe pain crises are typically managed with parenteral opioids and nonsteroidal anti-inflammatory drugs. Oxygen, intravenous fluids, and red blood cell transfusions are not typically prescribed unless clinically indicated.

What Is the Prognosis of Individuals Living With SCD?

Life expectancy for individuals living with SCD is approximately 54 years in the US, 20 years shorter than the general population. In sub-Saharan Africa, approximately 50% to 95% of children with HbSS disease die by age 5 years. A common complication of SCD is acute and chronic pain, the latter occurring in approximately 40% of adults with SCD. However, they are not more likely to develop addiction to pain medications than the general population. Other complications include acute chest syndrome, stroke, nephropathy, and retinopathy.

Table 2. Primary Prevention Recommendations for Sickle Cell Disease

Sickle cell disease complication	Pathophysiology	Screening evaluation	First-line prevention
Cognitive impairment and developmental delay	Anemia and vasculopathy of cerebral vessels	American Academy of Pediatrics and American Academy of Neurology surveillance screening tools[22]	No preventive strategies are available
Nephropathy	Sickling in the renal medulla	Urine microalbumin every year, starting at age 10 y[31]	No preventive strategies are available
Perioperative complications (especially acute chest syndrome)	Anemia and sickling	Assess independent risk of patient and type of surgery[30]	Preoperative RBC transfusion if undergoing general anesthesia lasting >1 h[30]
Retinopathy	Retinal ischemia with secondary neovascularization and hemorrhage	Dilated eye examination every 1-2 y, starting at age 10 y[31]	No preventive strategies are available
Septicemia from encapsulated organisms	Functional asplenia	Not applicable	Penicillin prophylaxis twice daily until age 5 y[a] Immunizations[a]
Stroke	Vasculopathy of major cerebral vessel(s) +/− moyamoya	Transcranial Doppler ultrasound every year, between ages 2-16 y[22]	Chronic RBC transfusions for high risk[b] Consider switching to hydroxyurea >1 y[b]
Silent cerebral infarct	Vasculopathy of cerebral vessel(s)	MRI of the brain, at least twice (early school-age and adulthood)[22]	No preventive strategies are available[c]

Abbreviations: MRI, magnetic resonance imaging; RBC, red blood cell.

[a] First-line prevention source, Thornburg et al.[31] Additional information regarding penicillin prophylaxis: if appropriately vaccinated and no history of invasive bacteremia or splenectomy. Additional information regarding immunizations: per immunization schedule for asplenia.

[b] First-line prevention source for chronic RBC transfusions, DeBaun et al[22] and for switching to hydroxyurea, Ware et al.[53] Additional information regarding both forms of first-line prevention: transcranial Doppler recommended for patients with HbSS, HbSβ^0-thalassemia, or heterozygotes with HbSC phenotype.

[c] Additional information: although no preventive strategies are available, data apply to HbSS or HbSβ^0-thalassemia only. MRI should be performed without sedation.

30%[20]; this regimen is also used to prevent recurrent ischemic stroke in adults with SCD (Table 2). Hemorrhagic stroke is most common in young adults with SCD and often related to vascular malformations; the value of an emergency exchange transfusion in this scenario is uncertain.[60]

Acute Anemia

Acute anemia in SCD is defined as an acute decrease in hemoglobin from baseline by 2 g/dL or greater.[50] Splenic sequestration of sickled RBCs in the spleen is the most common cause of acute anemia in children and occurs in patients as young as 2 months old. The lifetime prevalence is approximately 7% to 30%.[50] Acute anemia due to splenic sequestration typically presents with left upper-quadrant pain in conjunction with a rapidly enlarging spleen, thrombocytopenia (<150 000/μL), rapidly decreasing hemoglobin, and increased reticulocyte counts of as much as 25% above baseline.[61] Hypovolemia and shock may develop quickly. Emergency treatment with RBC transfusion is needed to maintain euvolemia and oxygenation. Close monitoring is required for hyperviscosity syndrome, which occurs when trapped RBCs are released from the spleen, which increases the circulating RBC mass and decreases blood flow, leading to ischemic end-organ injury, especially the brain. The incidence of this complication is uncertain. Recurrence rates of as much as 78% have been reported[62]; therefore, splenectomy should be considered after an acute episode, especially if severe. A second cause of acute anemia is an aplastic crisis, characterized by an acute decrease in hemoglobin plus a significant decrease in reticulocyte count from baseline, leading to a precipitous anemia since sickle RBCs last only 10 to 14 days.[63] Aplastic crises may be caused by a parvovirus B19 infection or an acute inflammatory illness and is treated with RBC transfusion.[50] Patients with acute anemia should be assessed for delayed hemolytic transfusion reaction up to 28 days after their last RBC transfusion.[31]

Gallstone Disease

Gallstone disease in SCD arises from pigmented stones secondary to RBC hemolysis. Gallstones affect approximately 12% of children aged 2 to 4 years and 43% of those aged 15 to 19 years.[21] Among adults, the prevalence is as high as 75%.[64] Cholecystectomy is indicated only if the patient has symptoms; a laparoscopic approach is preferred.[21]

Priapism

Priapism, defined as a painful erection of more than 4 hours, affects approximately 40% of males with SCD, starting in childhood.[65,66] Low blood flow due to venous congestion in the corpora cavernosa impedes blood outflow and causes priapism, a process resulting from RBC hemolysis, causing aberrant regulation of nitric oxide and impeding smooth muscle relaxation (Figure 1).[67] Many have intermittent or "stuttering" priapism (lasting <3 hours), which is a risk factor for the more severe ischemic priapism.[68] Initial treatment consists of supportive measures with oral fluids, warm showers, and walking. If there is no response after 4 to 6 hours, a stepwise approach is used consisting of intravenous fluids, analgesia, and local injection of sympathomimetics or corporal aspiration (with or without irrigation). If these treatments are not effective, urgent shunting between the corpora cavernosa and the glans of the penis may be needed.[69] RBC transfusion is not indicated to treat priapism.[65] Refractory or recurring priapism may cause scarring and erectile impotence.[65] For patients with recurrent stuttering priapism, prophylaxis with α-adrenergics, PDE5 inhibitors such as sildenafil, antiandrogens, and luteinizing hormone–releasing hormone analogues have been used[68]; however, RCT evidence does not support their use.[70]

Venous Thromboembolism

Venous thromboembolism is common in SCD.[71,72] One study of 67 122 admissions among 10 454 children with SCD reported that

1.7% developed venous thromboembolism during their hospitalization. Central venous lines, chronic kidney disease, history of stroke, and admission to intensive care were associated with venous thromboembolism.[73] Pharmacological thromboprophylaxis is indicated for hospitalized adults with SCD and should be considered for at-risk children.[74] Acute treatment of venous thromboembolism is the same as for the general population, although indefinite anticoagulation should be considered if there was only a minor provocation, such as prolonged trip by plane or arthroscopic surgery without immobility.[74]

Management of Chronic SCD-Related Complications

Chronic Pain

Chronic pain affects approximately 40% of adults with SCD,[18] includes nociceptive, neuropathic, and central components,[75] and requires a multimodal strategy to minimize adverse effects on quality of life.[18] Although caution should be used when prescribing opioid therapy, for some patients, opioids are necessary and well-tolerated. Tapering should be performed with caution in patients treated with chronic stable opioid doses to prevent overdosing and mental health crisis.[76] Opioid use disorder has not been a major issue in the SCD population, as evidenced by a stable volume of opioid prescriptions from 2009-2014.[77] Adjunctive therapies should be offered, including cognitive behavioral therapy and antidepressants.[18] The role of cannabis to manage chronic pain in SCD is unclear. Patients reported decreased use of prescription pain medicines while using marijuana,[78] but a randomized, placebo-controlled crossover trial of 23 patients with chronic pain showed no difference in mean pain rating over 5 days for vaporized cannabis,[79] and its effect on hospitalizations is mixed.[80,81]

Avascular Necrosis

Avascular necrosis occurs due to bone ischemia, affects approximately 11% to 22% of individuals with SCD,[82,83] and typically involves the hips, shoulders, and spine. Avascular necrosis may be associated with eventual bone collapse. Physical therapy may alleviate pain due to avascular necrosis.[84] Hip coring (removal of necrotic bone from the femoral head), with or without bone marrow aspirate concentrate injection, is used in some centers, although no RCTs exist in patients with SCD.[84-87] Joint arthroplasty may be necessary in approximately 5% of patients with SCD, at a median age of 36 years.[83]

Sickle Retinopathy

Sickle retinopathy occurs in nearly all adults with SCD, caused by retinal ischemia with secondary neovascularization and hemorrhage. Retinal detachment and central retinal artery infarction may occur.[88] Photocoagulation laser therapy decreases the risk of bleeding[89]; antivascular endothelial growth factor therapy has also been used in SCD.[90] Ophthalmologic examination every 1 to 2 years is recommended beginning by age 10 years.[31]

Sickle Nephropathy

Hyposthenuria, or the loss of renal concentrating ability, occurs early in life; yet its link to progressive kidney disease is not established.[91] The prevalence of microalbuminuria, defined as 30 to 300 mg/g occurs in approximately 16% of children and in approximately 33% of adults with SCD.[21] Annual assessment for albuminuria is recommended beginning at age 10 years.[19] RBC sickling in the renal medulla, a hypoxemic and acidotic environment, may lead to glomerular and tubular damage. For those with microalbuminuria or significant albuminuria (>300 mg/g), treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is recommended; although it is uncertain whether these therapies prevent kidney disease in people with SCD.[92] Patients with significant albuminuria should be referred to a nephrologist for full evaluation as chronic kidney disease may present with only slightly elevated creatinine values. Those who progress to kidney failure should be considered for transplant because allograft survival is equal to that in other populations.[19]

Leg Ulcers

Leg ulcers are considered due to vaso-occlusion of the skin, occur over bony prominences, and may develop without injury or underlying infection. The prevalence of leg ulcers among people with SCD is approximately 8% to 10% in the US and may be as high as 75% in Jamaica.[93] Patients should be referred to a wound care clinic. The value of chronic transfusions has not been established.[21,93]

Pulmonary Hypertension

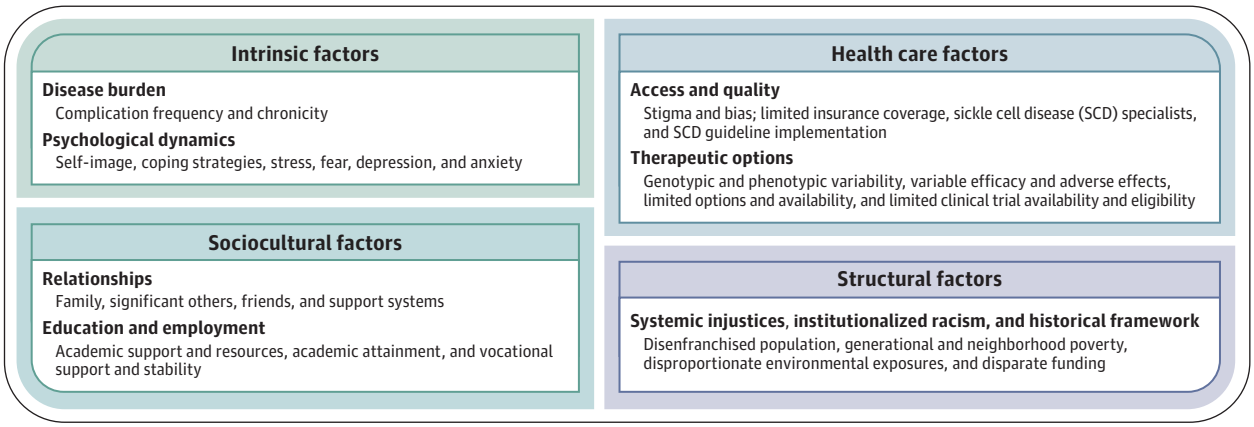
Pulmonary hypertension is characterized by elevated mean pulmonary arterial pressure estimated noninvasively by elevated tricuspid regurgitation velocity (normal <2.5 m/s) on echocardiogram; although definitive diagnosis requires right heart catheterization.[94] In one report, the 6-year mortality rate was 37% among 55 patients with SCD and pulmonary hypertension compared with 17% among 447 with SCD and without pulmonary hypertension.[95]

In patients with SCD, vascular endothelial damage from sickling, smooth muscle hypertrophy, and thromboembolic disease likely contributes to the increased prevalence of pulmonary hypertension. Using an older definition of mean pulmonary artery pressure (>25 mm Hg) to define pulmonary hypertension (the current definition is pulmonary artery pressure >20 mm Hg), 6% to 11% of SCD adults had pulmonary hypertension.[96] Current guidelines suggest against routine screening in asymptomatic patients due to lack of high-quality evidence of benefit.[19] Additionally, whether SCD-directed therapies alter the course of pulmonary hypertension is uncertain, and recent RCTs have not identified therapies to ameliorate pulmonary hypertension in SCD.[94]

Primary Prevention for Sepsis, Stroke, and Perioperative Complications in SCD

RCTs have demonstrated efficacy in the primary prevention of sepsis, ischemic stroke, and perioperative complications for surgeries requiring general anesthesia. In a trial of 215 children with SCD aged younger than 5 years, daily penicillin prophylaxis reduced pneumococcal septicemia by 84% compared with placebo, with 0 deaths in the penicillin group over a mean 15-month follow-up.[13] Annual screening with transcranial Doppler between ages 2 and 16 years in children with HbSS and HbSβ^0-thalassemia can identify increased blood flow velocity in the intracranial circulation, a marker for

Figure 2. Components of Living With Sickle Cell Disease (SCD)



Intrinsic factors such as the individual burden of recurrent SCD complications and related psychological dynamics are influenced by 3 extrinsic factors: sociocultural factors, health care factors, and structural factors. Health care factors are also influenced by whether the individual is cared for by an SCD specialist who adheres to national SCD guidelines. Therapeutic options are most often offered to people with HbSS and HbSβ^0-thalassemia genotypes, or other genotypes only after experiencing severe complications. There are only 4 approved SCD medications; efficacy and tolerability of each varies by individual. Furthermore, barriers to transplant include limited numbers of available donors and risks of toxicity. The structural factors shape both the sociocultural and health care experiences throughout the life span.[4,114]

ischemic stroke risk.[14] In a trial of 130 children with SCD and abnormal transcranial Doppler, RBC transfusions every 4 to 6 weeks decreased stroke incidence by 90% compared with standard care.[14] Transfusions are continued indefinitely and are associated with alloimmunization and iron overload. They may require placement of a long-term central venous catheter, with associated risk of infection and thrombosis. Children without severe vasculopathy may transition after at least 1 year of transfusions to hydroxyurea.[53] Preoperative RBC transfusion for patients who require general anesthesia for any procedure prevents postoperative complications. In an RCT of 67 children with SCD undergoing general anesthesia for low- and medium-risk procedures, preoperative transfusion reduced serious adverse events compared with no intervention (3% vs 30%). In the Transfusion Alternatives Preoperatively in Sickle Cell Disease trial, 91% of the serious adverse events were ACS.[15]

Reproductive Health in SCD

Pregnancy is associated with increased maternal and neonatal complications in SCD.[97] In one study of 177 pregnancies in people with SCD compared with 226 pregnancies in people without SCD, rates were higher for preeclampsia (15.7 vs 6.2%), urinary tract infection (7.9% vs 0.9%), and low birth weight (46% vs 19%) in those with SCD. ACS occurred in 22% of patients with SCD who were pregnant.[98] In addition, acute pain episodes are more common during pregnancy.[21] A meta-analysis of 11 cohort studies (of which 10 were retrospective and single center and 1 RCT involving 1291 people) reported that prophylactic RBC transfusions during pregnancy (targets including Hb 10-12 g/dL, hematocrit ≤35%, HbA 40%-50%, or HbS<25%-50%) were associated with lower rates of maternal and perinatal mortality.[99] However, most studies were at risk for selection bias, were small studies, and/or were more than 20 years old. Compared with pregnant people without SCD, pregnant people with SCD have higher rates of deep vein thrombosis (2% vs 0.3%) and pulmonary embolism (1.1% vs 0.1%) during the third trimester.[100] Hydroxyurea is typically discontinued during pregnancy and breastfeeding because of teratogenicity seen at high doses in animal studies, but harm to human fetuses at therapeutic doses for SCD is unclear.[20]

Because SCD is associated with hypercoagulability, estrogen-containing contraceptives should be typically avoided, and barrier methods and progestin-only contraception are typically preferred.[31,101] A recent literature review of 8 studies (2 RCTs, 2 nonrandomized trials, and 4 observational studies) suggested low-dose combination oral contraceptives were not associated with frequency of sickle cell crises. However, none of the studies examined the risk of thromboembolism.[101]

Male reproductive health problems are common in people with SCD, with as much as 24% developing hypogonadism, a syndrome of low testosterone, infertility, erectile dysfunction, and poor libido.[102,103] Sperm abnormalities may occur in as much as 90% of men with SCD, thought to be secondary to testicular infarction or hypogonadism. However, sperm abnormalities may also occur when hormone levels are normal.[104]

Prognosis

Current estimated life expectancy for patients with SCD in the US is 54 years compared with 76 years for patients without SCD.[105] In addition, young adults (aged 20-24 years) with SCD experienced increased mortality rates of 1.4/100 000 compared with 0.6/100 000 for adolescents (aged 15-19 years) with SCD.[106] Researchers from a single center in the United Kingdom used retrospective data from 450 patients with HbSS and HbSβ^0-thalassemia and estimated life expectancy at 67 years,[107] compared with 80.3 years for men and 84.2 years for women without SCD in London.[108] In contrast to higher-resource settings, 50% to 90% of children with SCD die before age 5 years in sub-Saharan Africa.[109]

Morbidity varies among patients with SCD. While approximately 1 in 4 individuals with SCD have no acute care encounters per year, approximately 1 in 5 have 3 or more per year.[110] Early adulthood (20s and 30s) is marked by fragmentation of care and loss of insurance coverage, which may lead to discontinuation of disease-modifying therapies such as hydroxyurea and chronic RBC transfusion, worsening SCD complications, and increased reliance on emergency department care, where patients with SCD may be treated by clinicians without expertise in SCD.[4] In contrast, continuity of care, especially when coordinated by primary care and hematology clinicians, has been associated with improved outcomes for patients with SCD.[111]

The experience of an individual with SCD is affected by various factors[112,113] including 4 interdependent elements: intrinsic, sociocultural, health care, and structural (**Figure 2**). Each individual with SCD manages daily SCD-related symptoms as well as mental health concerns, which in turn affect their daily lives, including education, work, and relationships.[115] An integral component of an individual living with SCD is the perceived inadequacy of many health care systems,[115] underscored by stigma, bias, bidirectional mistrust, lack of widespread use of evidence-based guidelines, paucity of therapeutic options, and poor access to SCD clinical trials.[114] In the US, structural systemic injustices and racism experienced by the Black population have perpetuated the disparate outcomes seen in individuals with SCD, as evidenced by the disparate funding between cystic fibrosis and SCD, resulting in fewer treatments and comprehensive care centers, and the inaccurate belief that Black patients perceive pain less than White patients.[4,114] These inaccurate perceptions result in longer wait times for pain relief, inadequate pain management, and the belief that patients with SCD are drug seeking.[4,114]

Limitations

This review has several limitations. First, quality of included literature was not evaluated. Second, some relevant references may have been missed. Third, there were few high-quality studies in SCD; therefore, some aspects of this review refer to guidelines that rely on expert opinion. Fourth, the lack of a formal SCD registry may result in imprecise estimates of SCD prevalence and its complications. Fifth, this review describes diagnostic and therapeutic approaches commonly used in high-resource settings, which may not be available to all clinicians caring for individuals with SCD.

Conclusions

In the US, approximately 100 000 people have SCD, which is characterized by hemolytic anemia, acute and chronic pain, acute chest syndrome; increased incidence of stroke, nephropathy, and retinopathy; and a life span that is 20 years shorter than the general population. While hydroxyurea is first-line therapy for SCD, L-glutamine, crizanlizumab, and voxelotor have been approved in the US since 2017 as adjunctive or second-line treatments, and hematopoietic stem cell transplant with a matched sibling donor is now standard care for severe disease.

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Drafting of the manuscript: All authors.
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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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