Title:

1.) From Innovation to Impact: Ensuring Continuous, Comprehensive Care in SCD

2.) Empowering the SCD Journey: New Therapies and the Path to Continuous Care

3.) SCD Treatment Frontiers: Closing Gaps with Novel Therapies and Coordinated Care

The Health Care Gap

Sickle cell disease (SCD) is a genetic blood disorder that alters the shape and function of red blood cells (RBCs), causing them to become rigid and crescent-shaped rather than round and flexible. These misshapen cells are prone to clumping and obstructing blood flow, leading to oxygen deprivation and widespread complications. SCD is a global health concern, with high prevalence in sub-Saharan Africa, India, the Mediterranean, and the Middle East. In the United States, it primarily affects individuals of African descent, impacting approximately 8% of the African American population, with an estimated 3 million people worldwide carrying the sickle cell trait. While advances in medical care have improved life expectancy in high-resource settings, nearly 90% of children with SCD in lower-income countries do not survive past age five.

At the molecular level, SCD results from a mutation in the HbS gene, in which valine replaces glutamic acid at the sixth position of the β-globin chain in hemoglobin. This structural change drives the pathophysiological cascade of hemoglobin polymerization, red cell sickling, and vaso-occlusion, leading to acute and chronic complications, including severe pain crises, fatigue, stroke, and organ damage. The mechanisms underlying these complications, particularly chronic pain and quality-of-life impairments, remain incompletely understood. Additionally, as patients age, their clinical needs evolve, necessitating proactive management strategies to address the transition from pediatric to adult care, mitigate the risk of disease-related complications, and optimize quality of life. However, gaps in clinical guidelines and access to comprehensive care continue to pose significant challenges.

To improve outcomes for individuals with SCD, it is essential for healthcare professionals to deepen their understanding of the disease burden, including its impact on pain, fatigue, and overall quality of life. Clinicians must also recognize the unmet medical needs in SCD, particularly during key life transitions, and integrate emerging therapies into treatment paradigms to address these gaps. Ongoing advancements in pharmacologic and curative therapies, such as gene editing and novel targeted agents, offer new hope for improving patient outcomes. Therefore, continued education for healthcare providers is critical to ensuring optimal, evidence-based care for individuals living with SCD across the lifespan.

Targeted Gap	Learning Objective	Practice Metric

Clinicians lack understanding on the evolution of healthcare needs of patients with sickle cell disease evolve as they transition from pediatric to adult disease management including challenges facing each patient population, disease progression, complications, and integrating multidisciplinary disease care to improve outcomes	Enhance clinician awareness of how the needs of patients with SCD evolve throughout their lifespan, recognizing key complications and challenges such as disease progression, transition from pediatric to adult care, and long-term management considerations.	Increase the ability of practitioners to guide patients with sickle cell disease as they transition from pediatric to adulthood disease management
Busy clinicians struggle to keep up to date on the latest advancements in SCD treatment and management due to the rapidly evolving treatment landscape	Appraise the emerging therapies for the management of SCD to improve outcomes for patients with SCD	Select the most appropriate intervention(s) from the emerging therapeutics for patients with SCD to optimize patient outcomes
Clinicians need education on evidence based, multidisciplinary care strategies and patient-centered approaches for SCD management to optimize patient outcomes	Recognize the best approach for shared decision-making and multidisciplinary care for each patient with SCD to improve patient long-term health and quality of life	Implement guideline based, multidisciplinary care plans for patients with SCD. This can be measured in increases in shared-decision making discussions, adherence to evidence-based treatment plans, referral to specialists when appropriate and improved patient-reported outcomes.

Medical Gap Analysis

Med Learning Group has undertaken an investigation to identify and analyze practice gaps and educational needs in the area of sickle cell disease. To this end, we reviewed multiple sources, including the medical literature, professional websites, outcomes measurement data, and consensus algorithms, to elucidate the knowledge gaps of hematologists involved in the diagnosis and management of patients with sickle cell disease.

Introduction

Sickle cell disease (SCD) is an inherited blood disorder of the red blood cells (RBCs). Normal red blood cells are round and flexible, allowing them to freely travel through blood vessels and deliver oxygen throughout the body. SCD red blood cells, however, are misshapen into a crescent shape, like a “C” or sickle. The sickle-shaped blood cells break apart easily, clump

together, and stick to the walls of blood vessels. This blocks blood flow, causing many serious health issues (The American Society of Hematology).

SCD affects people throughout the world and the United States. Most people with SCD live in sub-Saharan Africa, India, the Mediterranean, and the Middle East. Globally, an estimated 300,000 infants are born with SCD annually and 90% of children with SCD do not survive to adulthood in resource-poor countries. In Africa, approximately 1000 children are born with SCD daily and half die by the age of 5. Overall, approximately 3,000,000 people have the sickle cell trait. Risk factors for SCD include people of African descent, Hispanic-Americans from Central and South America, people of Middle Eastern, Asian, Indian, and Mediterranean descent (The American Society of Hematology).

While SCD is less common in the Americas, it is found in approximately 70,000 to 100,000 Americans, making it the most common inherited blood disorder. Higher rates of SCD are found in African Americans, in which it affects 8% of the population and occurs in 1 in 365 births (The American Society of Hematology). Nearly all children with SCD in the United States survive to adulthood, but it decreases their average lifespan by 20 years compared with the general population. In a study of a large US claims database from 2008 to 2016 analyzing lifetime survival among 94,616 individuals with SCD enrolled in Medicare or Medicaid, overall life expectancy was 52.6 years (95% CI: 51.9-53.4), declining to 35.4 years by age 18 and to 24.1 years by the age of 35 (Jiao 2022). Higher mortality also exists as individuals transition from pediatric to adult-focused health care systems (Kavanagh 2022).

From a pathophysiologic perspective, SCD emerges from hemoglobin polymerization due to protein misfolding resulting from a substitution of valine for glutamic acid at position 6 on chromosome 11. This change in shape results in vaso-occlusion that may result in end organ damage and painful SCD crises. Patients may experience vaso-occlusive crises, acute chest syndrome, splenic sequestration, stroke, infections, osteonecrosis, and psychosocial burdens resulting from the considerable physical and economic impacts of the disease. Multiple organ systems are affected, including the renal, pulmonary, biliary, and cardiovascular systems [Sedrak 2023].

Burden of Disease and Complications of Sickle Cell Disease

The damaged RBCs present in SCD cause the occlusion of blood vessels in almost every organ of the body and chronic hemolytic anemia, resulting in recurrent episodic acute clinical events. Acute pain is the most common, but accumulative organ damage also occurs. Repeated episodes of severe acute pain and acute chest syndrome characterize SCD, in addition to other complications, including stroke, chronic pain, nephropathy, retinopathy, avascular necrosis, priapism, and leg ulcers (Kavanagh 2022).

Pain is an overall result of SCD and the most common reason to seek acute or ambulatory care. Acute sickle pain is so severe that it is referred to as “vaso-occlusive sickle crisis,” or VOC, and is responsible for 95% of hospitalizations in patients with SCD (Ballas 2005). These events trigger pro-inflammatory pathways and result in the reduced bioavailability of nitric oxide (NO) and vascular endothelial dysfunction that underlies chronic organ damage in SCD pathology (Kavanagh 2022). VOCs may present as early as 6 months of age, and recurrent VOCs are linked to high morbidity, increased mortality, worsened health-related quality of life, and an increased number and duration of hospitalizations (Quinn 2013, Shah 2019, Drahos 2022, Houston-Yu 2003).

Patients with SCD are at risk for serious complications of stroke and acute chest syndrome (ACS). Acute ischemic or hemorrhagic strokes are a risk in people with SCD. ACS occurs in 10% to 20% of patients who are hospitalized with SCD and severe VOC, typically 1 to 3 days after being admitted (Miller 2012). Infections, hypoventilation, or fat embolism from infarcted bones can cause ACS, and it can present with fever, chest pain, tachypnea, wheezing, or cough. Due to the nature of ACS, it can rapidly progress to respiratory failure and death if not managed efficiently (Abboud 2020).

Evolving Needs of People With Sickle Cell Disease

SCD is a lifelong disease that is often diagnosed just after birth by neonatal screening. Thus, patients must transition from a child-focused to adult-focused health care system as they age. This is known as transition, and it is a vulnerable time for patients with SCD. The medical, psychosocial, and educational/vocational needs of adolescents must be considered as they transition. Unfortunately, even though the pediatric deaths have decreased over time, the peak mortality occurring during the early young adulthood years has remained steady (Saulsberry 2019). Barriers to health care transition include lack of trained adult providers, socioeconomic challenges, poor self-management skills or engagement, and disease progression.

Professional organizations recognize the importance of health care transition. The American Academy of Pediatrics, American Academy of Family Physicians, and the American College of Physicians were the first to develop an expert opinion and consensus statement on effective transition (American Academy of Pediatrics 2011). Later, the National Alliance to Advance Adolescent Health, in partnership with the Maternal and Child Health Bureau, created the Got Transition/Center for Health Care Transition Improvement. Got Transition is a resource that provides the 6 core elements of health care transition. The Six Core Elements serve as a framework for transition programs and comprise: 1) creating a transition policy, 2) tracking and monitoring progress, 3) assessing transition readiness, 4) planning for adult care, 5) transferring to adult care, and 6) integrating into adult care (Saulsberry 2019, Got Transition).

Still, an established metric for successful health care transition is currently not available and transition outcomes are not well studied. One retrospective analysis found that after 5 years of implementation of a modified SCD transition program, 32% of patients did not transition successfully and those at higher risk for an unsuccessful transition were patients with clinical markers of HbSC (compound heterozygous sickle and C hemoglobin) or HbSβ+ (compound heterozygous sickle and β-thalassemia plus) thalassemia not on chronic transfusions and who lived >20 miles from the adult center (Andemariam 2014). Other aspects that may affect transition, such as emotional and behavioral functioning, resilience, and health-related quality of life (HRQOL) have not been studied (Saulsberry 2019).

Managing Patients with Sickle Cell Disease

The clinical complexity and variable clinical course that the specific disease genotype cannot explain is one of the biggest challenges in managing patients with SCD. Both acquired and inherited factors contribute to the clinical complexity. It is important that disease severity classifications be assessed individually, even though laboratory prognostic factors and clinical phenotypes are described and analyzed. In addition, SCD should be managed with a holistic, interdisciplinary approach due to the wide range of disease complications (Cisneros 2020).

The only curative treatment for SCD is hematopoietic stem cell transplantation with stem cells from an immunologically matched sibling. Unfortunately, this is limited by the availability of matched donors and financial burden (Kavanagh 2022).

Pain management and control is a primary goal in patients with SCD. The American Society of Hematology (ASH) 2020 Guidelines for SCD: Management of Acute and Chronic Pain states that optimal treatment of VOC in SCD requires an individualized approach involving interdisciplinary care. The guidelines also recommend using a standard protocol to treat acute SCD pain in the acute care setting, which involves assessments within 1 hour of arrival and administration of analgesia with reassessment every 30 to 60 minutes for optimal pain control (Brandow 2020). Patient self-report is the gold standard for pain assessment (Brandow 2022). The guidelines also recommend a short course of nonsteroidal anti-inflammatory drugs in addition to opioids for acute main management. Ketamine infusion or regional anesthesia as adjunctive treatment for pain refractory to opioids alone is recommended. Adjunctive non-pharmacologic therapy suggestions include massage, yoga, transcutaneous electrical nerve stimulation, virtual reality, and guided audiovisual relaxation (Brandow 2020).

Blood transfusions with normal RBCs remain an effective therapeutic option for managing and preventing SCD complications, but this is not without limitations. Transfusions are not uniformly accessible and accompanied by risks of alloimmunization, hemolytic transfusion reactions, and transfusional iron overload. Hemolytic transfusion reactions most commonly occur in RBC alloimmunized patients and SCD patients. These patients are at high risk because of the mismatch in the donor pool (mostly Northern European descent) while SCD patients are mostly of African descent. In addition, evidence for the role of blood transfusions in managing acute or chronic complications is lacking (Cisneros 2020).

Deferiprone is an oral iron chelator traditionally used to treat iron overload in patients with thalassemia major, which often requires regular blood transfusions leading to excess iron in the body. Its role in SCD has been explored because patients with SCD may also experience iron overload due to frequent blood transfusions as part of their management, particularly those who develop complications such as chronic anemia. In the study LA38-0411 comparing deferiprone to deferoxamine in patients with SCD and other transfusion-dependent anemias, efficacy was measured by the change in liver iron concentration (LIC) over 12 months. The study included 185 patients, with 122 treated with deferiprone and 63 with deferoxamine. Most patients had SCD, and deferiprone demonstrated non-inferiority to deferoxamine, with a mean decrease in LIC of 4.13 mg/g dry weight for deferiprone compared to 4.38 mg/g dry weight for deferoxamine. After the first year, patients either continued with deferiprone or switched to it from deferoxamine, and continued treatment showed a consistent decrease in LIC over three years, from an average of 14.93 mg/g dry weight at baseline to 10.45 mg/g dry weight after three years. It is currently indicated for use for the treatment of transfusional iron overload in adult and pediatric patients aged 8 and over with SCD [Deferiprone PI]. An open-label study demonstrated that long-term deferiprone therapy was not associated with new safety concerns and led to continued and progressive reduction in iron load in patients with SCD [Elalfy 2023].

Allogeneic hematopoietic stem cell transplantation (HSCT) in the cure of SCD was first described in the literature more than 100 years ago and remains the only curative option for a small percentage of patients. Hematopoietic stem cell transplant is currently the only cure for SCD, but risks (e.g., graft rejection, GVHD), as well as the need to tolerate intensive conditioning regimens (eg, busulfan/cyclophosphamide), limit its use to high-risk young patients

[Ashorobi 2023; Bhalla 2023]. Advances in expanding access to HSCT focus on using megadose T-cell-depleted bone marrow with donor-derived CD8 veto T cells under reduced intensity conditioning to improve tolerance and engraftment rates in an ongoing phase I/II trial (NCT03622788) [Bhalla 2023].

Although patients with SCD still experience poor quality of life and reduced life expectancy from recurrent complications, progress has been made from early neglected research to current multi-pronged efforts targeting this genetic disorder [Ashorobi 2023]. Effective treatments for SCD include red blood cell exchange and hydroxyurea as first-line therapy, with additional available therapies of L-glutamine, voxelotor, and crizanlizumab as adjunctive agents [Abdel-Hadi 2023].

Hydroxyurea acts by decreasing sickling via fetal hemoglobin induction, while voxelotor reduces sickling through hemoglobin-oxygen affinity shifting, and crizanlizumab reduces vaso-occlusive events by inhibiting P-selectin interactions. With unique mechanisms, use of treatments in combination is one strategy under evaluation [Ribeil 2023]. Developments in pyruvate kinase activation and developments in gene editing show promise in treating SCD [Abdel-Hadi 2023].

L-glutamine decreases endothelial cell adhesion of sickle red blood cells (Niihara 2005) and was approved by the FDA in 2017. In a phase 3 study, L-glutamine reduced the number of pain crises by 25% and hospitalizations by 33% compared with placebo over 48 weeks (P = 0.005) (FDA).

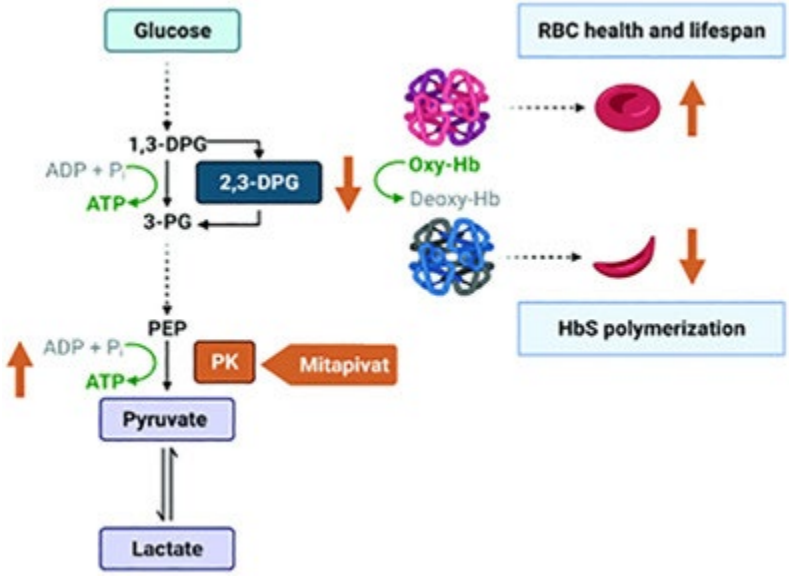
Crizanlizumab is a monoclonal antibody that binds to P-selectin and blocks interactions with its ligands, RBCs, and leukocytes. It is indicated to reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with SCD (Crizanlizumab PI). This approval is based the SUSTAIN trial, which is a phase 2, double-blind, randomized, placebo-controlled clinical trial of crizanlizumab in reducing vaso-occlusive crises in 198 patients with SCD. Patients received high-dose crizanlizumab (5 mg/kg), low-dose crizanlizumab (2.5 mg/kg), or placebo intravenously every 4 weeks for 52 weeks. The primary outcome of annual rate of pain crises was 45.3% lower with high-dose crizanlizumab versus placebo (median rate of yearly crises: 1.63 high-dose crizanlizumab versus 2.98 with placebo, P=0.01). Times to first and second crises were longer with high-dose treatment. Crizanlizumab was well-tolerated with arthralgia, diarrhea, pruritus, vomiting, and chest pain occurring in over 10% of patients at rates at least twice that of placebo [Ataga 2017]. The phase 3 STAND study, however, contrasts from the phase 2 SUSTAIN study results. The STAND trial, a phase 3, multicenter, randomized, double-blind study, evaluated crizanlizumab (5.0 mg/kg and 7.5 mg/kg) versus placebo in patients with sickle cell disease over one year. The primary endpoint, the annualized rate of vaso-occlusive crises (VOCs) leading to health-care visits, showed no significant difference between crizanlizumab (at either dose) and placebo. The incidence of adverse events was comparable across groups; however, grade 3 or higher adverse events and serious adverse events were more frequent in the 5.0 mg/kg crizanlizumab group compared to the 7.5 mg/kg and placebo groups (Abboud 2025). The SPARKLE trial is a phase III, multi-center, randomized, placebo-controlled, double-blind study assessing the efficacy and safety of crizanlizumab versus placebo with or without hydroxyurea/ hydroxycarbamide therapy (HU/HC), in patients with SCD aged 12 years and older with frequent vaso-occlusive crises (4-12 events in 12 months prior to the screening visit) (.

Voxelotor is a hemoglobin S polymerization inhibitor indicated for the treatment of SCD in adults and pediatric patients ages 4 years and older. It is approved under accelerated approval based

on an increase in hemoglobin (Voxelotor PI). In the phase 3 HOPE trial, 51% of patients had a hemoglobin response in the voxelotor group compared with 7% in the placebo group in the intention-to-treat analysis. Rates of grade 3 or higher adverse events were similar among the groups and not related to the use of voxelotor or placebo (Vinchinsky 2019). In the ongoing PROSPECT (NCT04930445) post-marketing observational prospective patient registry study the late 2023 study snapshot found voxelotor treatment was associated with increased hemoglobin levels and reductions in hemolytic markers while maintaining the safety profile found in the HOPE trial. (Shah 2024)

Mitapivat is an oral pyruvate kinase activator mitapivat that reduces HbS polymerization to increase intracellular 2,3-DPG level and promote hemoglobin deoxygenation by lowering oxygen affinity (**Figure: Mechanism of Mitapivat**) [van Dijk 2022]. In a single-center phase 1 study evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of multiple oral doses of the SCD drug mitapivat in 17 adults with sickle cell anemia, patients received doses of 5, 20, 50 or 100 mg twice daily for 2 weeks each, with a mean maximum hemoglobin increase of 1.2 g/dL at 50 mg twice daily. The most common drug-related adverse events were grade 1 or 2 in severity, and included insomnia and arthralgia [Xu 2021].

Figure: Mechanism of Mitapivat



[From: van Dijk MJ, Rab MAE, van Oirschot BA, et al. Safety and efficacy of mitapivat, an oral pyruvate kinase activator, in sickle cell disease: A phase 2, open-label study. Am J Hematol. 2022;97(7):E226-E229. doi:10.1002/ajh.26554]

Based on the results from the phase 1 study, the phase 2 ESTIMATE study evaluated whether increased glycolytic flux through treatment with mitapivat decreases 2,3-DPG levels and increases ATP levels and inhibits HbS polymerization, RBC sickling, and improves hemolytic anemia in patients with SCD. The safety and efficacy was evaluated, and the study provided proof of concept for mitapivat treatment in patients with SCD. A screening phase, an 8-week dose-finding period, and a 52-week fixed-dose extension period were included in the study. The study results showed that most treatment-emergent adverse events were grade 1 and transient. The most common reported treatment emergent adverse events (TEAEs) included headache (n=4, 44%), transaminase increase (alanine aminotransferase increased in n=4, 44%; aspartate

aminotransferase increased in n=2, 22%) and dyspepsia (n=2, 22%). No grade 3 or higher treatment-related TEAEs were reported. Efficacy results showed a significant reduction in Point of Sickling with a mean reduction of 9.7 ± 6.2 mmHg from baseline (*P* = 0.0032). An increase in Hb-oxygen affinity was also shown, along with a decrease in 2,3-DPG level (mean decrease of 3.4 ± 1.2 mg/gHb; *P* = 0.0003) and an increase in ATP/2,3-DPG ratio (mean increase of 0.19 ± 0.08; *P* = 0.0008). Hb level also increased upon mitapivat treatment (mean increase 1.3 ± 0.5 g/dL; *P* = 0.0003). Six patients (75%) had an increase of ≥1 g/dL from baseline, with the highest being 1.9 g/dL. Five patients (63%) reached this increase at day 28 on mitapivat 50 mg twice daily. In all patients, a significant reduction in laboratory markers of hemolysis (reduced absolute reticulocyte count by 40%, plasma total bilirubin by 55%, and lactate dehydrogenase by 29%) was found. Improvements in Hb levels and markers of hemolysis were observed regardless of hydroxyurea use or SCD genotype. Thus, treatment with mitapivat improves anemia, Hb-oxygen affinity, and sickling parameters, and reduces hemolysis in patients with SCD in the 8-week dose-finding period. An increase in Hb level of ≥1 g/dL from baseline was achieved in 75% of patients (van Dijk MJ 2022a).

Follow-up data were reported on the safety and efficacy of mitapivat treatment for up to 60 weeks and the results showed no treatment related TEAEs grade ≥3. Improvements in anemia, markers of hemolysis, Hb-oxygen affinity, 2,3-DPG levels and ATP/2,3-DPG ratio were also shown. Preliminary data on VOC rates with 1.5±1.3 days in the 2 years prior to starting study treatment were reduced to 0.5±0.7 days when weighting cases by follow-up duration (*P* = 0.021). SCD-related hospital admission days were reduced from 5.9±7.1 days to 1.6±3.1 days (*P* = 0.134) (van Dijk MJ 2022).

The FDA granted orphan drug designation to mitapivat for the treatment of patients with SCD (Agios 2020). Ongoing studies include the phase 2/3 RISE UP study (NCT05031780) evaluating the effect of mitapivat versus placebo on hemoglobin levels, as well as on reduction in or prevention of sickle cell pain crises [ClinicalTrials.gov NCT05031780; Pilo 2023]. In the phase 2 portion of RISE-UP, mitapivat for SCD met its primary endpoint, with statistically significant increases in hemoglobin response rates observed in both the 50 mg twice daily and 100 mg twice daily arms compared to placebo. Of the 79 patients enrolled, 46.2% in the 50 mg arm and 50.0% in the 100 mg arm achieved the primary outcome of a hemoglobin response, defined as an increase of ≥1 g/dL from baseline, versus 3.7% on placebo (p=0.0003 and p=0.0001 respectively). Annualized rates of sickle cell pain crises over the course of the 12-week study were less frequent in the 50 mg arm (0.83) and 100 mg arm (0.51) versus the placebo arm (1.71). Additional benefits were seen with mitapivat including reductions in hemolysis markers and annualized rates of pain crises. The safety profile was consistent with prior studies [Agios 2023]. Follow-up results of the phase 2 study established longer term proof of concept of PK activation as a potential novel therapy in SCD. In the 1-year study, 90% of patients with SCD aged ≥16 continued with mitapivat, showing sustained hemoglobin level improvement and reduced hemolysis markers. Mild adverse events were common, and there was one non-treatment-related death due to COVID-19. The study showed a significant reduction in vaso-occlusive events, improvements in adenosine triphosphate, and decreased 2,3-diphosphoglycerate ratio and hemoglobin-oxygen affinity, endorsing further mitapivat research (van Dijk 2023). Based on the positive phase 2 results, the 100 mg twice daily dose was selected for the phase 3 portion of the study. Enrollment for the phase 3 study was completed in October 2024, with more than 200 patients enrolled across study sites. Results from this pivotal phase are expected by the end of 2025 (Agios 2024).

A more detailed understanding of the switch from fetal to adult hemoglobin and identification of transcriptional regulators have allowed for potentially curative gene therapies to be discovered. Lovotibeglogene autotemcel (bb1111) is a gene addition therapy that consists of autologous transplantation of hematopoietic and proginator stem cells that have been transduced with the BB305 lentiviral vector, which encodes a modified functional anti-sticking β-globin gene. It is approved for patients ≥12 years of age with SCD and a history of vaso-occlusive events. In an phase 1/2 study(NCT02140554) and phase 3 study (NCT04293185) of patients <12 years of agethe median total Hb level increased from 8.5 g/dL to approximately 12.3 g/dL with reduced hemolysis markers in the 46 patients who received the infusion. Of the 34 patients who had evaluable VOEs, 30 achieved adjudicated complete resolution of VOEs and 32 achieved complete resolutions of severe VOEs (including hospitalization) in the 6-18 months post infusion. Of 46 patients 41 achieved globin response. (Kanter 2022, Rifkin-Zenenberg 2024). In December 2023, the FDA approved lovotibeglogene autotemcel for use in the treatment of patients aged 12 years and over with SCD and a history of vaso-occlusive events (FDA 2023).

The ongoing CLIMB SCD-121 trial is investigating the safety and efficacy of exagamglogene autotemcel (exa-cel) in patients with SCD. Exa-cel is an autologous cell therapy that employs nonviral methods to stimulate fetal hemoglobin production. This process involves ex vivo CRISPR–Cas9 gene editing at the erythroid enhancer region of BCL11A in the patient's hematopoietic stem and progenitor cells. Study results showed that treatment with exa-cel eliminated vaso-occlusive crises in 97% of patients with sickle cell disease for a period of 12 months or more (Frangoul 2024). The long-term follow-up study, CLIMB-131 has demonstrated promising results. New long-term follow-up data from the CLIMB-121 and CLIMB-131 studies demonstrate sustained clinical benefits and promising durability. In SCD, 93% (39/42) of evaluable patients with at least 16 months of follow-up were free from vaso-occlusive crises (VOCs) for at least 12 consecutive months (VF12), with a mean VOC-free duration of 30.9 months and a maximum of 59.6 months; the three patients who did not achieve VF12 still showed substantial reductions in VOC-related hospitalizations (91%, 71%, and 100%). Patients reported meaningful improvements in quality of life, including physical, emotional, social, and functional well-being. The safety profile remains generally consistent, and patients continue to show stable levels of fetal hemoglobin (HbF) and consistent allelic editing across ages and genotypes. (Vertex Pharmaceuticals Incorporated).

The pyruvate kinase activator, etavopivat, is an investigational oral agent that has been evaluated in animal studies and human studies. In healthy subjects, etavopivat significantly increased hemoglobin-oxygen affinity after 24 hours. Incubation of SCD patient red blood cells with etavopivat in vitro increased hemoglobin-oxygen affinity and reduced sickling under deoxygenated conditions (Schroeder 2022). A first-in-human phase 1 clinical trial evaluated the safety, pharmacokinetics, and pharmacodynamics of etavopivat, in 90 healthy subjects. Treatment decreased 2,3-diphosphoglycerate levels and increased adenosine triphosphate levels, while improving hemoglobin-oxygen affinity. Treatment-emergent adverse events were predominantly mild in severity and no participants discontinued due to safety issues. Pharmacodynamic effects persisted for 48 to 72 hours post-dose, supporting once daily administration (Forsyth 2022). The phase 2/3 HIBISCUS study is ongoing (NCT04624659) (ClinicalTrials.gov NCT04624659). The 52-week data from the phase 2 part of the trial indicate

that compared with placebo, etavopivat reduced the annualized VOC rate through Week 52, increased hemoglobin levels at Week 24, and improved hemolysis markers and patient-reported fatigue, suggesting potential clinical benefit. Etavopivat was well tolerated. Based on the overall data, proof of concept was established for etavopivat in SCD (Delicou 2024).

The novel anti-C5 monoclonal antibody crovalimab directly targets the complement-mediated process of veno-occlusive events and is under evaluation in the management of such events in patients with SCD in the phase 1b CROSSWALK-A clinical study, as well as the phase 2a CROSSWALK-C clinical study (Bartolucci 2022; Callaghan 2022; Hsia 2024). Crovalimab showed rapid and sustained complement inhibition with a promising safety profile in a Phase 1/2 trial for paroxysmal nocturnal hemoglobinuria (Röth 2020).

A phase 2a randomized, double-blind, placebo-controlled clinical trial investigated the efficacy and safety of 6 monthly subcutaneous injections of 300 mg canakinumab, an interleukin-1β blocking monoclonal antibody, in 49 pediatric patients aged 8 to 20 years with sickle cell anemia. Although the primary endpoint of prespecified reduction in pain episodes was not met, canakinumab treatment resulted in significantly reduced markers of inflammation, occurrence of sickle cell anemia-related adverse and serious adverse events, number and duration of hospitalizations, and trends for improvement in other clinical outcomes. Canakinumab demonstrated an acceptable safety profile with no treatment-related serious adverse events (Rees 2022).

An open-label, single-arm clinical trial evaluated the efficacy of 6 months of oral rifaximin therapy in reducing vaso-occlusive crises among 13 adult patients with SCD with a history of frequent crises. Primary outcomes of median number of crises and days requiring intravenous opioid analgesia during therapy were significantly lower than expected based on pre-treatment rates. Specifically, crises decreased from a median of 4.5 to 1 per 6 months and days requiring opioids fell from 25.5 to 9 days (Lim 2019). Concurrent shifts in intestinal microbiota and reductions in circulating aged neutrophils support the role of modulating gut pathophysiology in SCD (Dutta 2020). Orphan Drug Designation was granted rifaximin for the treatment of SCD in October 2020 (Bausch 2020).

The fully human monoclonal anti-P-selectin antibodies inclacumab demonstrated similar binding affinity to crizanlizumab and potency in inhibition of P-selectin ligand interactions in vitro [Geng 2020]. In addition, ex vivo dose-dependent inhibition of P-selectin-mediated cell adhesion was demonstrated using whole blood from patients with SCD (Tarasev 2022). In a phase 1 clinical trial evaluating the safety, pharmacokinetics, pharmacodynamics, and immunogenicity of single ascending doses of 20 mg/kg and 40 mg/kg of the anti-P-selectin monoclonal antibody inclacumab were reported in 15 healthy adult subjects. Inclacumab demonstrated dose-proportional pharmacokinetics and sustained inhibition of thrombin-receptor activated platelet-leukocyte aggregation for at least 12 weeks at both dose levels with no serious adverse events, drug-related adverse events greater than grade 1, or dose-limiting toxicities reported. Two subjects developed non-neutralizing antibodies without impacting safety or pharmacokinetics. Investigators selected a phase 3 therapeutic dose of 30 mg/kg every 12 weeks for further evaluation in reducing vaso-occlusive crises in SCD (Mayer 2021). The phase 3 THRIVE-131 (NCT04935879) study of inclacumab was completed in June 2024.

Isoquercetin, a flavonoid found in medicinal plants, has been considered as a potential therapy to inhibit sickle hemoglobin polymerization. Spectroscopic assays showed isoquercetin interacted with sickle hemoglobin through hydrogen bonding, and markedly decreased the rate

of sickle hemoglobin polymerization in a concentration-dependent manner and slowed red blood cell sickling [Syed 2020]. Previously, quercetin has been shown to reduce markers of erythrocyte and platelet activation were in 8 patients with sickle cell anemia and 8 controls [Lizarralde 2021]. Other data indicate efficacy in other conditions associated with hypercoagulability, including cancer. Specifically, a multicenter phase II clinical trial evaluated the efficacy of isoquercetin for reducing hypercoagulability in 57 cancer patients at high risk for thrombosis. Patients received oral isoquercetin at 500 mg or 1000 mg daily for 56 days. The 1000 mg dose significantly decreased D-dimer levels by a median of 21.9% ($p=0.0002$), meeting the primary efficacy endpoint. This dose also significantly reduced platelet-dependent thrombin generation by 57.2% ($p=0.004$) and soluble P-selectin levels by 57.9% ($p<0.0001$) [Zwicker 2019]. In a randomized, double-blind, placebo-controlled trial conducted from November 2019 to July 2022, 46 adults with steady-state SCD were assessed for the effects of isoquercetin on thromboinflammation markers. Although there was no significant difference in the primary outcome of plasma soluble P-selectin levels between the isoquercetin and placebo groups (isoquercetin: 0.10 ± 6.53 vs. placebo: 0.74 ± 4.54; P = .64), the isoquercetin treatment group showed significant improvements in several other biomarkers. Specifically, isoquercetin treatment significantly reduced whole-blood coagulation and collagen-induced platelet aggregation (P = .03 for both), and significantly inhibited inducible mononuclear cell tissue factor gene expression and plasma protein disulfide isomerase reductase activity (P = .003 and P = .02, respectively) (Lizarralde-Iragorri 2024).

Further studies of CRISPR-Cas9 therapy are ongoing. A single-arm, phase 1/2 clinical trial (NCT04443907) examined the safety and efficacy of autologous transplantation of CRISPR-Cas9 gene-edited CD34+ hematopoietic stem and progenitor cells targeted to disrupt the HBG1 and HBG2 γ-globin gene promoters in 3 participants with severe SCD. At 6 to 18 months follow up, all participants achieved stable engraftment and induction of fetal hemoglobin, with mean levels ranging from 19.0% to 26.8% of total hemoglobin and fetal hemoglobin–immunostaining erythroblasts representing 69.7% to 87.8% of red blood cells. Manifestations of SCD decreased in all participants during the study period (Sharma 2023).

Gap Analysis Summary

SCD is a genetic blood disorder prevalent globally. Unlike normal, round, and flexible RBCs, those in individuals with SCD are misshapen and sticky, leading to various health issues. Although the lifespan of individuals with SCD has extended into adulthood, they continue to face challenges such as complications and chronic pain. Access to quality healthcare and affordable treatments remains a significant hurdle for many affected by SCD. The mechanisms behind vaso-occlusion and the intricate pathophysiology of SCD-related pain, both acute and chronic, are still not fully understood. Patients are also at an increased risk for comorbidities, particularly cardiovascular issues, necessitating a multidisciplinary approach to care. The transition from pediatric to adult care is critical for aging patients, yet guidelines for this process are lacking. Hematopoietic stem cell transplantation and blood transfusions stand out as the most effective treatments, though they are costly and require precise matching, limiting their feasibility for many. Treatment strategies are evolving to include new pharmacotherapies. One such promising drug is mitapivat, an innovative allosteric activator of pyruvate kinase, showing safety and efficacy in treating various hemolytic anemias, including SCD. While initial results are encouraging, indicating its safety and tolerability, further research is essential to confirm its potential as a comprehensive treatment solution for SCD. Clinicians must stay up-to-date regarding the latest treatments and approaches in managing the lifelong condition.

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Learning Objectives

- Enhance clinician awareness of how the needs of patients with SCD evolve throughout their lifespan, recognizing key complications and challenges such as disease progression, transition from pediatric to adult care, and long-term management considerations.
- Appraise the emerging therapies for the management of SCD to improve outcomes for patients with SCD
- Recognize the best approach for shared decision-making and multidisciplinary care for each patient with SCD to improve patient long-term health and quality of life

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5 min.	**Introduction and Pre-Test**

30 min.	**Didactic Content Shared by Faculty Using Slides and Infographic Data**
	
	Burden of Disease and Complications (LO1)
	• Pain: acute and accumulative due to organ damage
	  ○ Vaso-occlusive sickle crisis: proinflammatory cascade and decreased nitric oxide
	  ○ Hospitalizations, increased morbidity/mortality, worse QoL
	• Stroke risk
	• Acute chest syndrome
	  ○ Causes leading to ACS
	  ○ Complications
	Evolving Needs
	• Challenges in Transitioning to Adult Care
	• Barriers to Effective Management
	• Current gaps in guidelines for managing the transition from pediatric to adult care systems and impact on patient care
	• Strategies for Improving Transition Outcomes
	Management and Emerging Therapies
	• Pain management, transfustions, iron chelation therapy
	• Types of strategies (eg, role of hydroxyurea as frontline therapy, as well as adjunctive use of L-glutamine, volelotor, and crizanluzumab)
	• Hematopoietic stem cell therapy
	• Mitapivat: ESTIMATE trial and RISE-UP trial
	• Gene therapy: lovotibeglogene and exagamglogene autotemcel: CLIMB trials
	• Etavopivat: HIBISCUS trial
	• Crovalimab: CROSSWALK-A/-C
	• Canakinumab: clinical trial
	• Oral rifaximin: orphan drug designation 2020
	• Inclacumab: THRIVE-131 trial
	• Isoquercetin:

15 min.	**Case Study Discussion** (sample cases listed below) • 6-year-old female diagnosed with sickle cell anemia at birth. Brought to ER with fever (101.8 F), fatigue and left leg pain for 2 days. Pallor and mild jaundice. Left thigh pain and swelling. Hb: 7.2 g/dL, elevated reticulocyte, elevated WBC count, pending blood cultures. Next steps? • 32-year-old male with known SCD. Hx of recurrent pain crisis. Non-compliant with hydroxyurea therapy. Severe chest pain, shortness of breath, and 24 hour duration of dry cough. SpO2; 88% on room air, bilateral crackles, Hb 8/1 g/dL. Next multidisciplinary steps?
10 min.	**Conclusions, Q&A, and Post-Test**

As shown below, each Day in the Life DocuSeries chapter follows the documentary-style model by interweaving the perspective of a patient with sickle cell disease and hematologists with didactic content related to the diagnosis, management, and treatment of sickle cell disease.

	Chapter 1	**Chapter 2**
2-3 min.	**Pre-Test** **Introduction by Jane Seymour**	
25 min.	**Interviews**: • Patient with sickle cell disease • Hematologist	**Interviews**: • Patient with sickle cell disease • Hematologist

	Didactic Content (placement to be determined by faculty) **Overview of SCD (LO1; LO2)** • Epdemiology and global impact • Genetic and molecular pathophysiology of SCD • Inflammatory pathways and thrombosis in SCD • Burden of disease (acute and chronic pain, vaso-occlusive crises, acute chest syndrome, stroke and neurological complications, organ damage) **Diagnosing SCD (LO1)** • Blood-based diagnostic methods • Molecular/genetic-based diagnostic methods • Discuss how sickle cells lead to vaso-occlusion, leading to organ damage and acute painful crises • Differential diagnostic considerations **Transition of Care: Pediatric to Adult Management (LO2)** • Challenges in Transitioning to Adult Care • Barriers to Effective Management • Current gaps in guidelines for managing the transition from pediatric to adult care systems and impact on patient care • Strategies for Improving Transition Outcomes	**Didactic Content (placement to be determined by faculty)** **Traditional Management Strategies for Patients with SCD (LO3; LO4))** • Need for patient-centered treatment plans and shared decision-making in SCD management • Types of strategies (eg, role of hydroxyurea as frontline therapy, as well as adjunctive use of L-glutamine, volelotor, and crizanluzumab) • Developments with the oral pyruvate kinase activator mitapivat, including the mechanism and results of the ESTIMATE trial and phase 2 portion of the RISE-UP trial • Developments with the oral pyruvate kinase activator etavopitvat • Further developments (eg, crovalimab, canakinumab, rifaximin, incalcumab, isoquercetin, and vivo CRISPR-Cas9 therapy) • Benefits and disadvantages associated with each strategy/unmet needs **Emerging Pharmacotherapeutic Treatment for Patients with SCD (LO3)** • Clinical profile of emerging pharmacotherapeutic treatment for patients with SCD • Potential place of emerging pharmacotherapeutic treatment option in algorithms for the management of patients with SCD • Biology of pyruvate kinase activators and rationale for use in the treatment of SCD
2-3 min.	Conclusion Post-Test	

**The content here is subject to change based on any new scientific data or publications that are released before or during this initiative.*

Each Case Escalation module includes pre-read materials, an introduction to the case, and a patient case as outlined below:

	Module 1	**Module 2**	**Module 3**
Pre-Read Materials (time	Pathophysiology and Burden of Disease (LO1) • Epidemiology and global impact	Transition of Management of Sickle Cell Disease (LO2)	Sickle cell disease treatment and clinical applications (LO3;LO4) • Developments with the oral pyruvate kinase

determined by learner)	• Genetic and molecular pathophysiology of SCD • Inflammatory pathways and thrombosis in SCD • Burden of disease (acute and chronic pain, vaso-occlusive crises, acute chest syndrome, stroke and neurological complications, organ damage) • Blood-based diagnostic methods • Molecular/genetic-based diagnostic methods • Discuss how sickle cells lead to vaso-occlusion, leading to organ damage and acute painful crises • Differential diagnostic considerations	• Challenges in transitioning to adult care • Barriers to effective management • Current gaps in guidelines for managing the transition from pediatric to adult care systems and impact on patient care • Strategies for improving transition outcomes • Need for patient-centered treatment plans and shared decision-making in SCD management • Types of strategies (eg, role of hydroxyurea as frontline therapy, as well as adjunctive use of L-glutamine, volelotor, and crizanluzumab)	activator mitapivat, including the mechanism and results of the ESTIMATE trial and phase 2 portion of the RISE-UP trial • Developments with the oral pyruvate kinase activator etavopitvat • Further developments (eg, crovalimab, canakinumab, rifaximin, incalcumab, isoquercetin, and vivo CRISPR-Cas9 therapy) • Benefits and disadvantages associated with each strategy/unmet needs • Clinical profile of emerging pharmacotherapeutic treatment for patients with SCD • Potential place of emerging pharmacotherapeutic treatment option in algorithms for the management of patients with SCD • Biology of pyruvate kinase activators and rationale for use in the treatment of SCD
1-2 min.	**Introduction & Pre-Test**		
10-12 min.	**Patient Case** (reviewed by faculty alongside the most important concepts from the pre-read materials) A 4-year-old patient of African descent with recurrent epidoes of pain in the extremeties and family history of sickle cell disease.	**Patient Case** (reviewed by faculty alongside the most important concepts from the pre-read materials) A 19-year-old patient with sickle cell disease recently aged out of pediatric care and is experiencing increased pain episodes and struggling to manage his disease while attending college.	**Patient Case** (reviewed by faculty alongside the most important concepts from the pre-read materials) A patient with sickle cell disease experienced frequent vaso-occlusive crises despite adherence fo hydroxyurea.
1-2 min.	**Conclusions & Post-Test**		

**The content here is subject to change based on any new scientific data or publications that are released before or during this initiative.*