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REVIEW

Management of Sickle Cell Disease Complications Beyond Acute Chest Syndrome

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Abstract: Sickle cell disease results in numerous complications that can lead to significant morbidity and mortality. Amongst them, acute chest syndrome is the leading cause of mortality. As a result, most providers are in tune with this complication and well versed with management. As sickle cell patients now live longer, they face a multitude of other complications that if left unattended, can lead to significant morbidity and mortality as well. It is critical to look beyond acute chest syndrome and adopt a more comprehensive approach to the management of the sickle cell patient.

Keywords: sickle cell disease, acute chest syndrome, complications

Introduction

Sickle cell disease (SCD), an inheritable blood disorder due to a point mutation in the beta-globin gene resulting in the substitution of valine for glutamic acid at the 6th amino acid, was first described over 100 years ago.[1–3] Since then, the complex pathophysiology has been elucidated from simply the red blood cell to a multicellular event to include the blood vessel itself.[3–5] This hemoglobin (Hb) gene defect is responsible for serious and life-threatening complications of hemolytic anemia, inflammation, an impaired immunity to encapsulated organisms and vascular occlusion (Figure 1).[6] Secondary complications to these include stroke, skin ulceration, priapism, acute and chronic organ damage, and a shortened lifespan.[7] SCD complications are elusive due to the underestimation of the impact of social barriers, the inability to measure pain, and the failure to look beyond the underlying pathology during painful events. In fact, 22% of deaths associated with SCD complications are preceded by a painful crisis.[8] More specifically, acute chest syndrome (ACS) has been one of the most devastating SCD complications with a high mortality rate if there is a delay in diagnosis or mismanagement across all age groups. As such, there is a heightened awareness of ACS among healthcare providers, specifically those in the acute care/emergency setting. We want to help providers shift beyond ACS to a more comprehensive management approach by highlighting the social barriers to quality of care and the other complex, yet elusive, severe and potentially life-threatening complications of SCD.

The management of SCD is finally transforming into a more comprehensive and diverse approach. Blood therapy and pain treatment were the mainstay of support therapy until 1998 when Hydroxyurea (HU) became the only Food and Drug Administration (FDA) approved drug that targeted the molecular pathogenesis.

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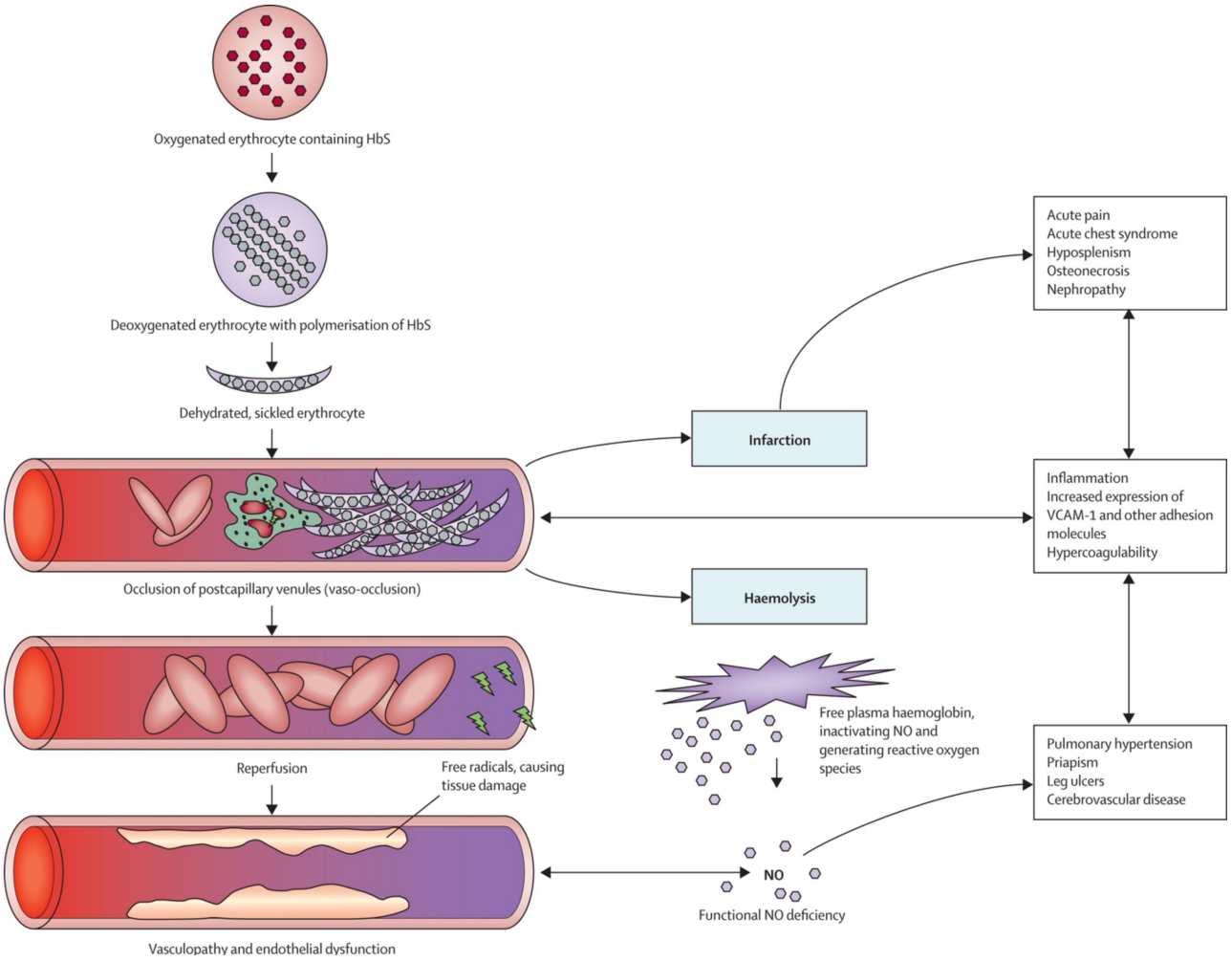

Figure 1 Pathophysiology of sickle cell disease.
Notes: Reprinted from Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010;376(9757):2018–2031, Copyright © 2010 Elsevier Ltd. Licensed under CC BY-NC-ND.[6]
Abbreviations: HbS, sickle hemoglobin; NO, nitric oxide; VCAM, vascular cell-adhesion molecule.

Elucidation of new pathophysiology has resulted in the evolution of new targeted drugs for SCD management.[1,2] There is now a transition from having one FDA approved drug over the past 110 years to a robust new arsenal of targeted drug development. Currently, there are over 30 novel pharmaceutical agents being studied and 3 have recently been FDA approved.[1,3,9–11] New targets for drug development in SCD include adhesion, antioxidation, inflammation, fetal Hb induction beyond HU, anti-sickling, anticoagulation, and opiate sparing drugs. In addition, we have expanded our approach from supportive care to curative procedures such as bone marrow transplant, gene therapy, and gene editing.

Until recently, the management of SCD has focused on the pathophysiology of the disease with less emphasis on addressing the complex social hardships which ultimately exists as barriers to quality care and management. Individuals with sickle cell disease navigate their lives through the hardships of associated complications such as acute chest syndrome and painful vaso-occlusive events while also facing a barrage of social barriers to quality care such as the transition from pediatric to adult care and health disparities. Now is the time to recognize that there is a need for a national movement to eliminate these barriers in order to truly ensure that the unmet social and medical needs are being addressed in the sickle cell population. Our goal is to review the management of the systemic complications of SCD beyond acute chest syndrome, pipeline novel agents, and health disparity gaps in order to help the health care system have a more heightened awareness of the underlying and elusive complications that if remain overlooked in the shadows of ACS may cause harm to individuals living with sickle cell disease.

Health Disparities

This is a time in which America is becoming more socially and consciously aware of the apparent unresolved consequences of systemic racism. A recent article in the New England Journal of Medicine (NEJM) highlighted racism and solutions in the US and its effect on SCD.[12] In the United States (US), the majority of people with sickle cell disease have a 30-year gap in life expectancy compared to the general population and are of African heritage, while on the other hand, there is a lower incidence in people of Hispanic, South Asian, South European, and Middle Eastern descent who are also affected.[7] These statistics play an important factor in the way those living with SCD experience real-life consequences of the health disparities that exist in our healthcare system.

The lack of national awareness, funding for research, therapeutic development, and social services for SCD in comparison to other conditions that are prevalent to a more universal racial demographic such as asthma, heart disease, breast cancer, colon cancer, and diabetes supports systemic racism as an underlying issue.[13] In fact, even among rare diseases this is true. The genetically acquired, life-threatening impact that SCD has on African Americans is similar to the impact that Cystic Fibrosis (CF) has on Caucasian Americans. Although SCD is more common than CF as it affects three times more Americans, it has been in its shadows with approximately ten times less funding, and has only one quarter of the number of FDA approved therapeutic agents.[14–16] Those living with SCD suffer barriers to quality care as there are profound healthcare gaps of socioeconomic status, racial discrimination, lack of sufficient federal funding, lack of consistent disease-specific access to quality care, and provider discord especially for pain management.[17–19] The long-standing history of stereotyping as opioid drug seeking fakers of true pain, mistreatment, neglect, and lack of quality care of individuals living with SCD, without a doubt illuminates how racial biases fundamentally obstruct justice in the form of human rights, the rights to proper healthcare, and quality of life.[12]

We must work together to put in place realistic policies and training to ensure that racial discrimination within the healthcare system, especially as it relates to the barriers to adequate healthcare for those living with SCD, is considered a reportable adverse event and given as much priority to prevent, as medication or surgical errors are given.[20–22] Our hope is to see all healthcare settings transform from a place of injustice, fear, and suffering into a place of holistic disease-specific, patient-centered care that provides safety, hope, and healing for those living with SCD.

Approach to Children and Transition to Adult Care

Central Nervous System (CNS) Complications

In children, cerebral vasculopathy is the most common CNS complication resulting from progressive inflammation and oxidative endothelial damage within intracranial vessels, leading to increased risk of transient ischemic events and infarctive strokes.[23,24] Long-term sequelae can range from mild cognitive or behavioral impairment to devastating neurologic effects or death. Screening for vasculopathy beginning at age two is recommended,[25] as well as early initiation of disease modifying therapy to mitigate anemia and endothelial damage.

Another less-common complication that can present with acute neurologic symptoms is acute cranial bony infarction associated with intracranial hemorrhage and/or thrombosis. Cranial bony infarcts are believed to result from diploic vascular disruption due to extramedullary hemopoiesis.[26,27] In addition, periosteal elevation following an infarctive episode may result in bleeding and hematoma formation. This constellation of complications is uncommon but should remain on the differential even when an acute stroke is suspected, as acute neurosurgical intervention may be required to prevent significant morbidity or mortality.

Cardiovascular Complications

Many children may present with clinical murmurs due to hyperdynamic blood flow and mild to moderate left ventricular hypertrophy. Pulmonary hypertension and cardiomyopathy due to iron overload may not be clinically apparent until adulthood. Screening echocardiograms are not routinely recommended in children unless new symptoms or new clinical findings are noted on exam.[28]

Aplastic Crisis

Parvovirus –B19 is an erythrotropic virus that selectively targets human red blood cells and their precursors.[29] In patients with SCD, this can lead to life-threatening anemia due to abrupt cessation of erythropoiesis. Features are new or worsening signs of anemia, with an acute drop in hemoglobin and reticulocytopenia in the absence of

blood loss or sequestration. Urgent recognition and transfusion are necessary to prevent circulatory failure and death.

Splenic Complications

Splenic complications in children can include impaired immunity to encapsulated organisms such as *Streptococcus pneumoniae, Neisseria meningitides* and *Salmonella* species, leaving patients prone to life-threatening infections such as pneumonia, meningitis, osteomyelitis and sepsis. As a result, all febrile illnesses are considered medical emergencies until proven otherwise in infants and under-immunized children. Routine childhood vaccines are monitored and usually administered through primary care providers, with the addition of extended pneumococcal and meningococcal vaccines as standard of care. The initiation of prophylactic antibiotics in early infancy has significantly decreased the morbidity and mortality historically associated with these infections.

Acute splenic sequestration of red cells and/or platelets is another potentially fatal complication in children. Autosplenectomy is less common in children who are initiated on disease-modifying therapy early in life, and therefore this complication may be seen in older children and teenagers. Reviewing splenic palpation and signs of anemia are an important component of anticipatory guidance for parents, with the need for urgent red cell transfusion if signs of circulatory failure.

Gastrointestinal Complications

Vaso-occlusion can occur in intra-abdominal vessels leading to acute abdominal pain as a presenting sign. A thorough evaluation for other causes of acute abdomen may be unrevealing in these patients. These vaso-occlusive episodes are managed appropriately with pain control and hydration.

Sickle hepatopathy is a broad term for a range of hepatic complications from mild liver dysfunction to chronic liver failure and cirrhosis. Acute vaso-occlusive events within hepatic parenchyma may present with fever, jaundice, transaminitis and intense abdominal pain similar to the acute abdominal presentation above.[30] Management is supportive with hydration and pain control. Intrahepatic sequestration, or trapping of red cells within the liver, can also lead to intense pain and transaminitis. A large, tender liver may be felt on examination or noted on ultrasound, in addition to an acute drop in hemoglobin. Management is also supportive with transfusion as needed for symptomatic anemia.

Secondary hemochromatosis may be seen in transfused patients with poorly managed transfusional iron overload with occasional transaminitis noted. However, chronic hepatic or cirrhotic changes are an uncommon presentation in childhood.

Other differentials for acute abdominal pain and jaundice with or without fever in SCD are cholelithiasis and/or cholecystitis resulting from pigmented gall stones due to chronic hemolysis leading to obstruction of hepatobiliary bile flow.[30] Obstructive gall stones may also lead to intrahepatic cholestasis or extra-hepatic obstruction and acute pancreatitis. Elevated inflammatory markers, transaminases and bilirubin beyond baseline are suggestive of this diagnosis. While a focused abdominal ultrasound may identify inflammation and/or stones, magnetic resonance or endoscopic cholangiopancreatography are more sensitive in making a diagnosis. Urgent evaluations by gastrointestinal and surgical teams will help determine the need for urgent cholecystectomy vs antibiotics and conservative management with endoscopic stone removal.

Peptic ulcers are not uncommon in children with SCD, especially given frequency of non-steroidal anti-inflammatory drug use. Chronic central to upper abdominal pain that may be relieved by antacids or food, may require evaluation and treatment by a gastroenterologist.

Constipation is another frequent complaint in children, usually as a side effect of narcotic pain medication use. An age-appropriate bowel regimen is recommended for use at home and inpatient, although an aggressive bowel cleanout may occasionally be required.

Genitourinary Complications

Sickle nephropathy results from hypoxia and ischemia within renal medullary vasculature, resulting in micro-infarction and papillary necrosis. In addition, intravascular hemolysis produces free hemoglobin which can lead to oxidative damage in renal tubular cells. Nephropathy can vary in presentation from microalbuminuria and proteinuria to significant renal dysfunction and renal failure. Patients at higher risk are those with significant anemia and hemolysis. Annual screening starting at age 10 can identify microalbuminuria as an early sign of nephropathy. The use of angiotensin-converting enzyme (ACE) inhibitors, in addition to SCD-modifying therapy has been shown to minimize progression of nephropathy.[28]

In male patients, priapism represents an unwanted persistent painful erection that can present at any age. Conservative measures to redirect penile blood flow such as exercise, distraction, or warm baths are recommended as first line. Pseudoephedrine is an α-adrenergic agonist that may be used

as needed at home for intermittent episodes. Painful episodes lasting more than 4 hours are considered an urologic emergency.[31]

Musculoskeletal

Osteonecrosis can occur in anywhere including cranial bones as described above but are frequently found at the ends of long bones in patients with SCD. These may present as persistent localized pain beyond a typical vaso-occlusive episode with or without fever. Magnetic resonance imaging can aid in the diagnosis, although necrotic bone may be difficult to distinguish from osteomyelitis. Conversely, necrotic bone can serve as a nidus for bacterial overgrowth and osteomyelitis. Management is usually conservative with pain medications, unless associated with osteomyelitis or bone abscess requiring debridement.

Avascular necrosis (AVN) is most often located within the femoral head and can be a source of chronic debilitating pain in teenagers and young adults. Management is usually conservative in growing patients, although this complication continues to be a reason for frequent emergency room visits, impaired mobility and diminished quality of life. Long-term pain management is individualized, and often involves a combination of narcotics, non-steroidal anti-inflammatories and other adjunct medications. Unfortunately, optimal pain control may be difficult to achieve in some patients. Conservative surgical techniques such as core decompression and stem cell injection into the joints have had variable results, and many of these patients inevitably require hip-replacement surgery.[32]

Transition to Adult Care

There are many significant challenges that are unique to the teenage and young adult population as they transition from pediatric to adult care models. Transition in itself is a complication of SCD that requires specific attention and should not be overlooked. It represents yet another example of an important social component that is not only in the shadows of ACS but also exists as a barrier to quality care. Individuals living with SCD are vulnerable to the concept of "falling through the cracks" within the healthcare system, as they transition from pediatric to adult care. Young adults (aged 18–30 years) account for the highest healthcare utilization compared to other age groups (greater than twice the amount of emergency room visits per year, higher inpatient stays and highest frequency of acute care visits).[33]

Many recurrent childhood complications as described above will persist through the transition years. In addition, early presentations of significant organ damage may start to manifest such as cardiomegaly, pulmonary hypertension, sickle nephropathy and proteinuria, avascular necrosis and chronic pain syndromes. In addition, young adults with a history of strokes in childhood, may present with cognitive deficits that become more notable as the need for health independence and self-efficacy increase. Young patients on chronic transfusions may have difficulty with continuation of transfusion as they transition, if significant iron overload or red cell alloimmunization have developed. Other undesirable outcomes of an unsuccessful transition to adult care include loss of health insurance coverage, limited availability of adult hematologists experienced in SCD, and inability to attend appointments due to transportation issues. The management of SCD beyond ACS must include transition to adult care in order to achieve a truly comprehensive approach to caring for those living with SCD.

Approach to Adults

Sickle cell disease is no longer a disease of childhood, as patients now live well into adulthood. As they progress into adulthood, they are faced with more challenges – increasing rate of comorbidities in the setting of a paucity of skilled and willing adult providers to care for them.[34] Acute complications in adulthood include vaso-occlusive crisis (VOC), acute chest syndrome, acute splenic sequestration, aplastic crisis, acute osteomyelitis, cerebrovascular disorders, hepatobiliary issues, acute kidney injury (AKI), priapism, venous thromboembolism (VTE) and multi-system organ failure. Chronic complications include avascular necrosis (AVN), chronic pain, leg ulcers, ocular issues, renal complications and cardiac complications (pulmonary hypertension, diastolic dysfunction). It is important to note that the aging sickle cell population may also experience the typical complications of adulthood and aging (mental health issues, diabetes, gout, hypertension, degenerative joint disease, autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus). These are managed similar to the general population.

Acute chest syndrome is a life-threatening complication in patients suffering from SCD, and the leading cause of mortality. It is usually present at a higher incidence in patients with homozygous SCD, triggers hospital admissions and can have catastrophic consequences.[35] Defined by an expert panel as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest x-ray, it could also present with multiple infiltrates, hypoxemia

conducive to respiratory failure with or without pain syndrome and associated organ failures due to hyper hemolysis, sequestration and/or microvascular occlusions.[36] Pneumonia or systemic infections, fat embolism and pulmonary infarction represent the most common mechanisms, with atypical bacterial or viral infections accounting for most cases.[37]

The standard management for ACS is the use of broad-spectrum antibiotics as well as supportive care such as adequate oxygenation, incentive spirometry, pain control and reduction of abnormal hemoglobin concentration. Decreased concentration can be achieved with transfusions (simple) or with emergent red cell exchange for severe cases. Oxygenation should satisfy patient's needs and provide symptoms relief with adequate oxygen saturation. Progressive delivery should be started with nasal canula, venturi mask or High Flow Oxygen vs noninvasive ventilation systems. If these options do not achieve desirable effects medical care should proceed to mechanical ventilation with endotracheal tube intubation for support. Patients requiring mechanical ventilation have usually bilateral alveolar infiltrates consistent with pulmonary edema which can be cardiogenic; related to fluid overload consequence of the aggressive hydration to control hemoglobin S concentration; or non-cardiogenic with Acute Respiratory Distress Syndrome (ARDS) physiology secondary to sepsis or Transfusion Associated Lung Injury (TRALI).

Acute pain/VOC is the hallmark of SCD and the most common reason that the sickle cell patient seeks medical attention. Triggers include hypoxia, dehydration, extremes of temperature, acidosis and infection. It is largely managed with pain medications and supportive care.

Pain can also be chronic which is usually multifactorial, ranging from actual tissue/organ damage (due to AVN, leg ulcers) to neuropathic and idiopathic pain. Chronic pain is defined as ongoing pain that is present on most days for over 6 months.[38] Opioids are most commonly used. However, use of non-opioid and non-pharmacological modalities such as meditation, massage, acupuncture, etc are garnering more attention.[39,40]

VTE defined as a deep vein thrombosis or pulmonary embolism (PE), has a high incidence in SCD patients. Up to 12% of patients have a VTE by age 40 years.[41] Diagnosis and treatment are as in the general population.

Multisystem organ failure is an acute, fatal complication of SCD, defined as acute decompensation of 2 or more of the following organs: lungs, kidney, liver. It is usually associated with VOC, fever, and an acute drop in Hb and/or platelets. An urgent exchange transfusion is indicated, as well as supportive care such as supplemental oxygen/mechanical ventilation and renal replacement therapy if warranted.

Leg ulcers are an uncommon complication in children and rare under 10 years of age.[42,43] However, they pose a significant source of pain and distress in the adult with SCD. Risk factors include hemoglobin SS genotype, severe anemia and increased hemolysis. Leg ulcers usually present initially in the second decade of life and may be present for several years.[44] They may arise following a traumatic event to the skin, or spontaneously.[45] The most common site is around the medial and lateral malleoli of the ankle. Management is via a multidisciplinary approach which includes wound debridement and dressings, pain management and infection control.[44]

Ocular manifestations in SCD include proliferative and non-proliferative sickle retinopathy, hyphema, vitreous hemorrhage and central retinal artery occlusion (CRAO). Retinopathy screening is conducted by annual dilated eye exams from age 10 years. Management of proliferative retinopathy involves laser photocoagulation. CRAO is a medical emergency and requires an urgent exchange transfusion.

Splenic complications, aplastic crisis, acute osteomyelitis, acute cerebrovascular events, hepatobiliary issues, renal complications, priapism, AVN, and cardiac complications are covered in detail in a previous section.

Reproductive Health and Pregnancy in Sickle Cell Disease

In men with SCD, reproductive issues include sperm abnormalities, hypogonadism and erectile dysfunction (ED). Up to 91% of males with SCD experience sperm abnormalities manifesting as low sperm count and density, poor motility, and increased abnormal morphology.[46] Puberty in general is delayed in SCD. Hypogonadism is present in up to 24% of males with SCD and may manifest as poor testosterone production, infertility, ED and poor libido.[47] There remains a debate as to whether it is of primary or secondary etiology. Current therapies include testosterone injections and clomiphene.

ED may result from repeated episodes of priapism. One study demonstrated a 21.4% prevalence of priapism, and 22.2% prevalence of ED within that cohort, 92.3% of the cohort experiencing repeated episodes of priapism.[48] Management options include penile implants/prostheses.

In women with SCD, reproductive issues include delayed puberty, choice of contraception and pregnancy-related complications. Puberty in SCD females is delayed by up to 2.4

years compared to the normal population.[49] The menstrual cycle is also associated with increase in pain. Choice of contraception remains a source of debate. Due to the theoretical risk of clot predisposition with the estrogen-containing products, providers usually opt for progestin only pills/injectable and IUD. Depo-Provera which also decreases the number of cycles has been helpful for those patients who experience a crisis with their cycles.

Pregnancy in SCD is associated with increased risk of VTE, pre-eclampsia/eclampsia, increased pain crisis, preterm labor, prematurity, intra-uterine growth retardation (IUGR), small for gestational age (SGA) babies and fetal demise.[50] Pregnancy in SCD is considered high risk and a multidisciplinary approach inclusive of a sickle cell expert and a knowledgeable maternal fetal medicine provider is recommended for close monitoring during this delicate period. The decision to prophylactically transfuse or not is usually provider dependent. Management of acute and chronic pain also poses a challenge with pregnancy in SCD. A retrospective study demonstrated that compared to non-SCD pregnant mothers who are on methadone for opioid dependence, neonatal abstinence syndrome (NAS) occurs at a similar rate in SCD pregnant mothers on daily opioids, and at a significantly lower rate in those treated episodically with opioids.[51] However, opioids must be used judiciously in pregnancy to mitigate these adverse effects on the fetus/newborn.

Sickle Cell Disease in the Age of COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), also known as COVID-19 has now affected over 38 million patients worldwide.[52] Our knowledge base is rapidly evolving, but this virus poses a significant concern in our patient population. Sickle cell disease is an immunocompromised condition which puts patients at risk of complications from respiratory infections. Our experience of this particular complication is currently limited and a standard of care has not been established; however, there have been several collaborative groups that have aimed to identify patterns and suggest management options for our patients.[53,54]

Early publications have suggested increased morbidity in SCD patients. A recent French case series described outcomes of eighty-three inpatient individuals.[55] The experience reported an ICU admission rate of 20%, fifty-three percent of which required mechanical ventilation, including two patients which required extracorporeal membrane oxygenation, and two patients who died in the ICU with COVID-19 pneumopathy. This underscores the importance of early identification and intervention in our patients. The challenge is that there is significant overlap in presenting signs and symptoms of patients with ACS and COVID-19 infection. Fever, shortness of breath, cough, and myalgias are all overlapping symptoms of ACS, pulmonary embolus, vaso-occlusive crisis, and SARS-CoV-2.

The Medical College of Wisconsin has developed a voluntary international registry of patients with SCD and COVID-19 infection in the hopes to better understand its pathophysiology.[54] Interestingly, the most common presenting sign, in the approximately 350 patients registered, is pain, with less than 30% of patients presenting with pneumonia. This highlights the importance of looking beyond ACS and becoming hypervigilant of possible COVID-19 infection in patients without respiratory complaints. Recent case reports also support VOC and fever as the most common reported symptoms in patients with SCD and COVID-19 infection.[56] Other respiratory viral infections often trigger "sickle cell crisis", and COVID-19 appears to have a similar effect. It is imperative that we obtain SARS-CoV-2 PCR testing in any patient with SCD presenting with ACS and/or VOC symptoms.

The lack of large published studies investigating this disease also poses a challenge in the management of known COVID-19 infected patients. A recent review of the literature of nineteen SCD patients with COVID-19 reported from December 2019 to May 2020 described a varied combination of management all similar to those used in the treatment of ACS.[57] Their approach included supportive care with hydration, analgesics, empirical broad-spectrum antibiotics, red blood cell exchange, and simple blood transfusions. Oxygen-support ranged from low flow (2 L/min) to high flow, non-invasive and mechanical ventilation in critically ill patients. A single dose of tocilizumab (8 mg/kg) was reported in 2 cases (adult and pediatric) with success.

The American Society of Hematology has provided community resources as guidance for the management of suspected COVID-19 in patients with SCD.[58] A useful checklist has been developed in collaboration with ED physicians. Suggested interventions include supplemental oxygen to raise pO2 >94%, judicious fluid replacement and avoidance of fluid bolus as this may exacerbate pulmonary edema, broad-spectrum antibiotics after blood cultures if febrile, macrolide in addition to a third-generation cephalosporin in the event of pneumonia, vancomycin if there is concern for line or skin infection. Any patient with

COVID-19 who develops respiratory symptoms should have a type and cross available. Transfusion recommendations include simple transfusions if hemoglobin drops by more than 2 g/dL from baseline, or for patients with respiratory compromise with a goal hemoglobin of approximately 10 g/dL. If the hemoglobin is greater than 10 g/dl admissions should be transferred to an institution where exchange transfusion is available due to the risk of hyperviscosity with further simple transfusions. If patients are discharged home, close follow up is needed with telemedicine or in person visits within 24 hours. Patients should have a low threshold to return to the ED, especially if dyspnea worsens and should be provided with a pulse oximeter if possible.

Further management to consider during the age of COVID-19 includes the use of bronchodilators. The most common comorbidity reported in patients with SCD and COVID-19 is asthma.[54] Many institutions have suspended the use of nebulizers due to the risk of aerosolizing virus particles, however metered-dose inhalers should be used as replacement when appropriate. Additional management should also follow institutional standards of care for managing SCD and fever. These may include evaluation for typical seasonal viral infections and empiric oseltamivir, until influenza is ruled out; adequate pulmonary toileting, which includes ambulation as tolerated as well as incentive spirometry. Good pain control is also especially important to reduce atelectasis.

Lastly, it is of particular importance to address COVID-19-associated coagulopathy. Patients with sickle cell disease exhibit a baseline hypercoagulable state and are at an increased risk for venous thrombosis and pulmonary embolism. Some symptomatic patients may benefit from a PE protocol spiral computed tomography (CT) scan during work up. All children and adults hospitalized with SCD and COVID-19 should receive prophylactic anticoagulation dosing or "intermediate intensity" dosing (enoxaparin 0.5mg/kg twice daily), unless the risk of bleeding outweighs the risk of thrombosis. Inpatients should also have close monitoring of disseminated intravascular coagulation (DIC) markers (PT, aPTT, PTT, hepzyme, thrombin time, fibrinogen, D dimer) and inflammatory markers (CRP, ferritin, fibrinogen, IL-6, factor 8) to address thromboembolic risk throughout hospitalization.[58]

Sickle cell disease is a chronic medical condition requiring a multidisciplinary approach with continued "maintenance care" and constant education. It is of utmost importance that these interactions and collaboration continue during this global pandemic. Telemedicine has become an excellent tool to continue chronic sickle cell maintenance while aiming to avoid exposure. It is important to provide virtual appointments when possible rather than canceling regular maintenance appointments. It is also imperative to educate our patients on the importance of physical distancing, masking, and proper handwashing for the prevention of further spread.

Old and New Therapies

Blood Transfusion

Blood transfusion was the first therapy used in SCD, even at a time when the pathophysiology was still poorly understood.[59] Transfusions (simple and exchange transfusions) have remained a critical therapeutic and prophylactic intervention in sickle cell disease to date. Transfusion exerts its effect by dilution of Hb-S containing red blood cells (thereby decreasing the percentage of the abnormal Hb S), and increasing the oxygen carrying capacity of blood.[60] Therapeutic blood transfusions have been used for several indications such as: ACS, stroke, acute symptomatic anemia, aplastic crisis, splenic and hepatic sequestration, sickle hepatopathy, central retinal artery occlusion, and multisystem organ failure. Several randomized clinical trials have demonstrated the efficacy of prophylactic/chronic blood transfusions in primary and secondary stroke prevention, pre-operative management, and pregnancy.[61–67]

In addition to the above indications, providers have also utilized blood transfusions to alleviate other sickle cell disease complications, though not supported by concrete evidence. Before embarking on a chronic blood transfusion regimen with a patient, the potential benefits must be weighed against risks such as iron overload, red cell alloimmunization, transfusion reactions, and blood-borne viral infections.

FDA Approved Drugs

There are currently 4 FDA approved drugs for sickle cell disease, most gaining approval since 2017.

Hydroxyurea

Hydroxyurea, approved in 1998, was the first FDA-approved drug for sickle cell disease. It gained approval based on the randomized clinical trial that demonstrated decreased rates of vaso-occlusive crises, increased median time to first and second crises, and decreased rates of acute chest syndrome.[68] Initially approved for adults >18 years with sickle cell anemia, in 2017 it gained approval for children >2 years of age, based on an open-label trial conducted with pediatric patients.[69]

Hydroxyurea is a ribonucleotide reductase inhibitor that inhibits DNA replication. Its mechanism of action is not completely understood, but it is known to induce fetal hemoglobin (Hb F), which in turn inhibits intracellular Hb S polymerization and prevents sickling within the red blood cells.[70] In addition to increased Hb F synthesis and decreased Hb S polymerization, effects include increased Hb synthesis, decreased neutrophil count, hemolysis, RBC membrane damage, endothelial cell activation and adhesion, to mention a few.[71]

Endari (l-Glutamine)

L-glutamine is a conditionally essential amino acid; during periods of stress and severe illness, the body's production becomes insufficient. It is required for the synthesis of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), and indirectly regulates the metabolism of glutathione. NAD and its reduced form, NADH are involved in maintaining redox balance and sickle red cells have a low redox ratio compared to normal red cells.[72] The mechanism of action of l-glutamine in SCD is not fully understood but it has been shown to increase NADH in sickle RBCs, which is believed to reduce oxidative stress.[72] L-glutamine gained FDA approval in 2017 based on a randomized trial that demonstrated significantly reduced pain crises and hospitalizations in the drug group.[72] It is approved for sickle cell patients of all genotypes, age 5 years and above. This was hailed as the first SCD drug approval in almost 20 years since Hydroxyurea. However, concerns about patient accessibility and adherence have been reported.[73]

Adakveo (Crizanlizumab)

Crizanlizumab is a monoclonal antibody against the adhesion molecule P-selectin. P-selectin, expressed on the surface of endothelial cells mediates abnormal adhesion of sickle RBCs to the endothelium, and this process is implicated in the painful vaso-occlusion in SCD.[74] A randomized trial demonstrated significantly decreased rate of vaso-occlusive crises, and prolonged time to first and second crises on Crizanlizumab.[75] This led to its FDA approval in 2019 for sickle cell patients of all genotypes, age 16 years and above.

Oxbryta (Voxelotor)

Voxelotor is a small molecule that binds to the alpha chain of hemoglobin, increasing Hb S affinity for oxygen, delaying Hb S polymerization and preventing RBC sickling.[76] In essence, it is an HbS polymerization inhibitor.[77] A randomized trial demonstrated significantly higher percentage of participants with a Hb response (>1 g/dl from baseline), fewer instances of worsening anemia and significant reduction in baseline markers of hemolysis with the drug.[77] This led to its FDA approval in 2019 for sickle cell patients of all genotypes, age 12 years and above.

Curative Modalities

Bone Marrow Transplant

Bone marrow transplant (BMT) works by replacing the faulty "machinery" in the sickle cell patient: the marrow which produces abnormal sickle RBCs is replaced with a functioning marrow that produces normal RBCs that do not sickle. The first successful BMT as a cure for SCD was serendipitous. A young pediatric patient with both leukemia and sickle cell anemia underwent transplant as treatment for her leukemia, with resultant cure of her sickle cell disease as well.[78] This was followed by a quick succession of other institutional reports of their experience with BMT as a cure for SCD.[79–83] Outcomes have been impressive with overall and event free survival well above 90% with HLA-matched sibling donors.[84,85] Expanded donor pools such as matched unrelated donors and haploidentical donors have been explored, albeit at an increased risk of graft rejection and increased mortality.[86]

Gene Therapy

Gene therapy portends a potential for cure for SCD but is still in its nascent stages. Viral vectors are employed as vehicles to introduce a therapeutic anti-sickling coding gene (gene addition), to induce Hb F via silencing of repressors of the gamma-globin gene (Hb F induction), or to correct the sickle mutation via genomic engineering tools such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 (gene correction).[87] The first successful gene therapy for SCD was reported in 2017, using a lentiviral vector-mediated addition of an anti-sickling beta-globin gene into the subject's hematopoietic stem cells.[88] Currently, multiple other clinical trials are in progress to investigate the efficacy of gene therapy in SCD. Anecdotal reports of successful gene therapy have been highlighted.[88–90] However, caution must be exercised, because as with every thorough clinical research, the ongoing trials need to be concluded to determine the efficacy of the intervention.

Pipeline Agents

In contrast to a few decades ago, there now exists numerous ongoing clinical trials with novel agents for the treatment of sickle cell disease in the pipeline.[91] Table 1

Table 1 Ongoing Clinical Trials of Novel Agents in Sickle Cell Disease

Drug	Mechanism	NCT Number (Study Acronym)	Clinical Trial Phase
Anti-sickling agents			
Nicotinamide with oral THU and Decitabine	Hb F induction	NCT04055818	Phase I
Panobinostat		NCT01245179	Phase I
Metformin		NCT02981329	Phase I
Gum Arabic		NCT04191213	Phase II/III
Voxelotor (formerly GBT-440)	Allosteric modifier (to the R-state)	NCT04247594	Phase II
		NCT04335721	Phase I/II
		NCT04188509	Phase III
		NCT03573882	Phase III
		NCT04400487	Phase IV
		NCT02850406 (HOPE Kids)	Phase II
		NCT04218084 (HOPE Kids 2)	Phase III
AG-348 (Mitapivat sulfate)	Allosteric activator of RBC pyruvate kinase-R	NCT04000165	Phase I
FT-4202		NCT03815695	Phase I
SCD-101	RBC ion transport channels	NCT02380079	Phase Ib
Memantine (NMDAR antagonist)		NCT03247218	Phase IIa/IIb
Anti-adhesion agents			
Crizanlizumab (formerly SEG-101)	P-selectin antagonist	NCT03814746 (STAND)	Phase III
		NCT03938454 (SPARTAN)	Phase II
		NCT04053764 (STEADFAST)	Phase II
		NCT03264989	Phase II
		NCT03474965	Phase II
Isoquercetin		NCT04474626	Phase II
IVIG	Blockade of fcγrIII receptors	NCT01757418	Phase I/II
Imatinib	Tyrosine kinase inhibitor	NCT03997903 (IMPACT)	Phase I
SHP655 (recombinant ADAMTS13)	ADAMTS13 protein replacement	NCT03997760 (RAISE-UP)	Phase I/II
CSL889	Hemopexin replacement	NCT04285827	Phase I
Anti-inflammatory agents and nitric oxide-related drugs			
Defibrotide	Antithrombotic, anti-inflammatory	NCT03805581	Phase II
Mometasone	Anti-inflammatory	NCT03758950 (IMPROVE2)	Phase II
Docosahexaenoic acid (SC411)		NCT02973360 (SCOT)	Phase II

(*Continued*)

Table 1 (Continued).

Drug	Mechanism	NCT Number (Study Acronym)	Clinical Trial Phase
Arginine	Increased NO production	NCT02447874	Phase I/II
		NCT02536170	Phase II
Sodium Nitrite (topical)		NCT02863068	Phase II
Riociguat (soluble guanylate cyclase stimulator)	Vasodilator	NCT02633397	Phase II
IMR-687 (selective phosphodiesterase-9 inhibitor)		NCT03401112	Phase II
		NCT04474314	Phase II
		NCT04053803	Phase II

Notes: Adapted from Rai P and Ataga KI. Drug Therapies for the Management of Sickle Cell Disease [version 1; peer review: 2 approved]. F1000Research 2020, 9(F1000 Faculty Rev):592 (https://doi.org/10.12688/f1000research.22433.1), licensed under CC-BY 4.0 (https://creativecommons.org/licenses/by/4.0/).[91]
Abbreviations: THU, tetrahydrouridine; NMDAR, N-methyl-D-aspartate receptor; IVIG, intravenous gammaglobulin; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.

reviews this information. Completed or terminated trials, as well as trials in gene therapy are omitted.

Conclusion

The complications and comorbidities of sickle cell disease are numerous. Acute chest syndrome remains the leading cause of mortality and must be taken keenly. However, various other sickle cell complications deserve attention, in order to ensure the wellbeing of the patient as a whole and improve their quality of life. Other complications that may lead to long-term comorbidities should not be overlooked. Whether it is acute chest syndrome, pain, or a social challenge like reduced quality of care due to racial discrimination, there is a need to look beyond the usual, and shift focus to a more comprehensive approach to the patient.

Multidisciplinary management as with management of leg ulcers or the pregnant sickle cell patient should be emphasized, so as to attain more favorable outcomes. Reproductive counseling can generate a profound impact on the burden of sickle cell disease. Interventions as simple as a routine annual ophthalmologic exam to rule out sickle cell retinopathy can have grave consequences if neglected in a subgroup of patients. Cerebrovascular events should be promptly followed up with intense rehabilitation to preserve residual gross and fine motor functioning. Updated vaccinations, to provide added protection against encapsulated organisms should be ensured. Routine health maintenance as in the general population, such as yearly flu vaccines, colonoscopies, and mammograms should be highly encouraged as well.

It is refreshing that several novel agents are in the pipeline, to deal with the underlying cause of sickle cell disease. Experimental gene therapy also promises a potential cure, if successful. However, true success in the clinical trials realm will entail successful implementation of their significant findings beyond the developed world – in low- and middle-income countries, where most of the world's sickle cell population reside. As discussed with the complications of sickle cell disease, the race to the cure must be attained on a global level.

Finally, sickle cell disease is a clear example of the fact that systemic racism is an unfortunate truth in American society. Therefore, we as healthcare providers should serve as role models to the rest of the country by dedicating ourselves to eradicating racially motivated healthcare disparities such as inadequate access to healthcare, suboptimal patient care, limited funding for research and therapy development, and poor quality of life in order to truly go beyond to new heights in the management of SCD.

Disclosure

Dr Ugochi O Ogu received Consultancy fees from Vertex Pharmaceuticals, outside the submitted work. Dr Patricia Adams-Graves is Consultant and speaker for Novartis and GBT, outside the submitted work. The authors report no other conflicts of interest in this work.

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