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Pediatric sickle cell disease: past successes and future challenges

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Once a fatal disease of childhood, more than 95% of patients born today with sickle cell disease (SCD) in developed countries are expected to survive into adulthood, largely because of improvements in supportive and preventive care (newborn screening, penicillin prophylaxis, transcranial Doppler (TCD) screening). Hydroxyurea (HU) therapy, the only oral medication currently available to prevent SCD complications, has become more widespread over the past 20 y. The NHLBI recommends that HU be offered to all patients with HbSS beginning at 9 mo of age, and the recently published Abnormal TCD with Transfusions Changing to HU (TWiTCH) trial has shown HU as an acceptable alternative to transfusion therapy for patients at high risk of stroke. While hematopoietic stem cell transplant (HSCT) is a curative option for SCD, less than 25% of patients have a suitable donor. Alternative stem cell sources from unrelated donors and haplo-identical donors are currently under investigation as are gene therapy trials. This review will focus on early efforts to elucidate SCD pathophysiology as well as supportive and preventive care improvements. Findings from recent multi-center studies (Silent Infarct Transfusion (SIT) Trial and TWiTCH) will be summarized. Finally, HSCT trials and gene therapy will be reviewed.

Sickle cell disease (SCD) was first described in 1910 in a dental student from the West Indies presenting with recurrent painful episodes, hemolytic anemia, and jaundice (1). On microscopic review of the patient's blood smear, Dr. James Herrick and his intern, Dr. Ernest Irons, identified red blood cells in the shape of a sickle, for which the disease was named (2,3). Over the course of the last century, much has been learned about SCD. While childhood mortality has decreased to less than 5% in the United States (4), life expectancy has not increased in the past 30 y, remaining at half that of the average American (5,6).

Called the first molecular disease by Linus Pauling in 1949 (7), SCD is used to describe individuals who have hemoglobin S (HbS) as the predominant form of hemoglobin. HbS is caused by a single point mutation in the β-globin gene substituting a hydrophobic valine amino acid for glutamic acid at position 6 of the β-chain, making HbS molecules much more likely to polymerize in states of dehydration or acidosis. HbS polymerization causes the characteristic sickle shape change and downstream effects of sickling. Two-thirds of people with SCD produce only HbS as the adult form of hemoglobin, because they are either homozygous for the HbS mutation (HbSS) or compound heterozygous for the HbS and β^0thalassemia mutations (HbSβ^0thalassemia), and have sickle cell anemia (SCA) (8,9). The remaining third of patients with SCD have other compound heterozygous β-globin chain mutations, the two most common being HbSC and HbSβ^+thalassemia (8,9). SCA is typically more severe than other forms of SCD (10).

The purpose of this review is to summarize supportive care initiatives that have led to improved survival for pediatric patients with SCD in developed countries as well as the recent discoveries for additional uses of hydroxyurea (HU) and transfusion to prevent SCD-associated morbidity (see **Table 1** for a summary of the supportive care guidelines for pediatric SCD patients from the 2014 NHLBI Evidence Based Management Guidelines (11)). We will also highlight recent breakthroughs in curative therapies for SCD, namely hematopoietic stem cell transplant (HSCT) and gene therapy.

SICKLE PATHOPHYSIOLOGY

The sickled erythrocyte is highly susceptible to hemolysis and removal by the spleen resulting in a shortened lifespan of 12–16 d, one-tenth that of a healthy erythrocyte containing normal adult hemoglobin (HbA) (12,13). Symptoms of SCD are related to anemia, vaso-occlusion by irreversibly sickled cells that interrupt blood flow, cell adhesion that results in vasculopathy, and vasoconstriction from decreased nitric oxide availability (**Figure 1**). Inability of rigid, sickled cells to pass through the microvasculature leads to hypoxia of the tissues and painful vaso-occlusive episodes (VOE) in the acute setting as well as tissue damage with ischemia–reperfusion pathophysiology. Intrasplenic sickling leads to eventual splenic autoinfarction which is responsible for an increased risk of infection with encapsulated organisms in people with SCD. Sickled erythrocytes and reticulocytes have adhesion proteins on their surface which damage vascular endothelium, leading to vasculopathy and vasospasm (14,15). Endogenous nitric oxide, produced in the endothelium from arginine, maintains

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Table 1. Summary of pediatric SCD supportive care from 2014 NHLBI evidence-based management guidelines

Health maintenance strategies	STRONG recommendations	Moderate or weak recommendations
Antibiotic prophylaxis	Administer Penicillin VK prophylaxis twice daily in children with SCA. Dose of 125 mg twice daily <3 y and 250 mg twice daily >3 y.	Stop Penicillin VK prophylaxis at age 5 y once immunization series complete *unless* patient experienced surgical splenectomy or pneumococcal bacteremia.
Immunization	Immunize all ages and subtypes of SCD against S. *pneumoniae.*	
Retinopathy screening	Refer all persons with SCD for dilated eye examinations by an Ophthalmologist beginning at age 10 y.	
Neuroradiologic screening	Screen children with SCA by annual TCD per STOP protocol from age 2 y to at least 16 y. Do not screen subtypes SC and Sβ+thalassemia.	Do not perform screening of asymptomatic children by MRI or CT.
Pulmonary care		Do not perform screening pulmonary function tests in asymptomatic children.
Pulmonary hypertension		Screen symptomatic people with SCD with echocardiography.
Nephropathy		Screen annually for proteinuria beginning at age 10 y.
Hydroxyurea	Offer Hydroxyurea maintenance therapy to all children with SCA over age 9 mo regardless of clinical severity.	Consider Hydroxyurea therapy in adolescents and adults with HbSC or HbSβ+thalassemia who have recurrent SCD-related pain interfering with daily activities or quality of life.

SCA, sickle cell anemia; SCD, sickle cell disease; TCD, transcranial Doppler.

patent vessel walls. In people with SCD, nitric oxide is consumed by plasma free hemoglobin and degraded by arginase which is released from hemolyzed sickle erythrocytes (16). The resultant vascular dysfunction plays a prime role in the manifestations of stroke, pulmonary hypertension, leg ulceration, sickle nephropathy, and priapism (17). More recently, altered interactions between the vascular endothelium, neutrophils, platelet, and sickled erythrocytes have been identified as direct promoters of sickle vaso-occlusion and inducers of a chronic inflammatory state in people with SCD (18).

IMPROVED SURVIVAL IN CHILDHOOD—IMPACT OF EARLY IDENTIFICATION AND SUPPORTIVE CARE MEASURES

Newborn Screening, Infection Prophylaxis, and Fever Management

Newborn screening for hemoglobinopathies began in the state of New York in 1975 with expansion to 40 other states in the 1980s and 1990s and became mandated in all 50 states in 2006 (19). Prior to universal newborn screening, penicillin prophylaxis, and vaccination against encapsulated organisms, infection was a common cause of death in children with SCD; median survival was 20 y of age in 1970 (20). The randomized, placebo-controlled trial of prophylactic penicillin (PROPS) revealed that twice daily penicillin prophylaxis in infants and children with SCD reduced the rate of invasive pneumococcal disease by over 80% (21). The risk of invasive pneumococcal disease in children with SCD has decreased 70–90% since the addition of the protein-conjugated pneumococcal vaccine series (PCV, Prevnar) in early infancy (22,23). The PROPS study included children with HbSS and HbSβ^{0}thalassemia, the two sickle genotypes with the highest risk of pneumococcal infection because of splenic autoinfarction. Children with HbSC and HbSβ$^+$thalassemia have less splenic dysfunction (24,25) and, therefore, a decreased risk of invasive pneumococcal disease, leading the NHLBI Evidence Based Disease Management Guidelines Committee to state that practitioners should "consider withholding penicillin from children with HbSC and HbSβ$^+$thalassemia unless they have had a splenectomy." (11) A recent survey of pediatric SCD experts reported that almost 85% of centers routinely prescribe penicillin prophylaxis to patients with HbSC and HbSβ$^+$thalassemia (26).

Infections cause more morbidity, disseminate more rapidly, and are more difficult to eradicate in persons with SCD because of impaired clearance of bacteria from the circulation and opsonization of bacteria. Infections can precipitate aplastic crisis, exacerbate hemolytic events, and precipitate VOEs. All people with SCD, regardless of genotype, should be considered functionally asplenic because of the auto-infarction of the spleen that occurs at a very young age from recurrent intravascular sickling. Education of families and patients about the importance of emergency evaluation for fevers ≥ 101° F (11) as well as the appropriate management with blood culture and timely administration of an antibiotic (such as ceftriaxone) effective against S. *pneumoniae,* H. *influenza,* and other encapsulated, rapidly multiplying organisms has further decreased the morbidity and mortality from infection (27,28).

Splenic Sequestration

Acute splenomegaly, pallor, or lethargy can be the first clinical signs of a potentially life threatening splenic sequestration crisis in young children with SCD (29). Repetitive intrasplenic sickling and local infarctions eventually result in a fibrotic, nonfunctional spleen. Ninety-five percent of children with SCA will have complete auto-infarction of the spleen by age 5 y (30).

Splenic sequestration refers to an acute condition of intrasplenic sickling and pooling of large amounts of blood. Children

between ages 5 mo and 2 y represent most cases of splenic sequestration (31). During severe sequestration crisis, the blood-filled spleen may enlarge to the point of filling the entire abdomen, the hemoglobin may drop acutely (at least 2 g/dl below baseline with compensatory reticulocytosis (31)) and can result in hypovolemic shock and death within hours of onset if not detected early (31). Given the potential rapid course and high mortality rate, spleen palpation is taught to all parents of newly diagnosed infants with SCD and reviewed at subsequent clinic visits. This early and repeated parent education occurring as a result of universal newborn screening has reduced mortality from splenic sequestration by nearly 10-fold (31). Early detection of splenomegaly by parents allows for prompt treatment with volume expanders and blood transfusion to reverse the hypovolemic shock, can help remobilize the blood sequestered in the spleen and lead to regression of the splenomegaly over a fairly short period of time. Due to overall lower level of sickle-related infarctions (24,25), the spleens of older children and young adults with HbSC or HbSβ+thalassemia may remain enlarged or retain the ability to enlarge, placing them at risk for sequestration continuing into adulthood (32,33).

Transcranial Doppler and Stroke

Transcranial Doppler ultrasound (TCD) is a noninvasive screening tool to identify children with SCA who may be at increased risk for stroke. TCD measures the flow velocity through the cerebral arterial circulation, particularly the internal carotid and middle cerebral arteries. Increased flow velocity correlates with the presence of a narrowed vessel or segment; velocities of ≥ 200 cm/sec are strongly associated with increased risk of stroke (34). Prophylactic chronic monthly blood transfusions to reduce HbS concentration significantly decrease the risk of overt stroke in children with abnormal TCD velocities (35). Prior to 2016, transfusions and chelation therapy were continued indefinitely because the STOP 2 (Optimizing Primary Stroke Prevention in Sickle Cell Anemia) trial showed that discontinuation of transfusions caused reversion to abnormal TCD values and, in some cases, overt stroke (36). The recently published Abnormal TCD with Transfusions Changing to HU (TWiTCH) trial has shown HU as an acceptable alternative to transfusion therapy for patients at high risk of stroke with no evidence of cerebral vasculopathy on brain MRI/MRA (37). The TWiTCH trial is discussed in more detail in the HU section of this review.

MANAGEMENT OF ACUTE COMPLICATIONS

Painful Vaso-Occlusive Episodes

Painful VOEs are caused by ischemic tissue injury from obstruction of blood flow by sickled red blood cells and regional hypoxia and acidosis, which perpetuate the sickling process. VOEs usually last 4–10 d but can persist for weeks (38). Hypoxia, infection, dehydration, acidosis, menstruation, sleep apnea, and exposure to cold temperatures can precipitate VOE. Upregulation of adhesive and hemostatic properties of endothelial cells by certain viruses may explain how viral infections often precipitate VOE (39).

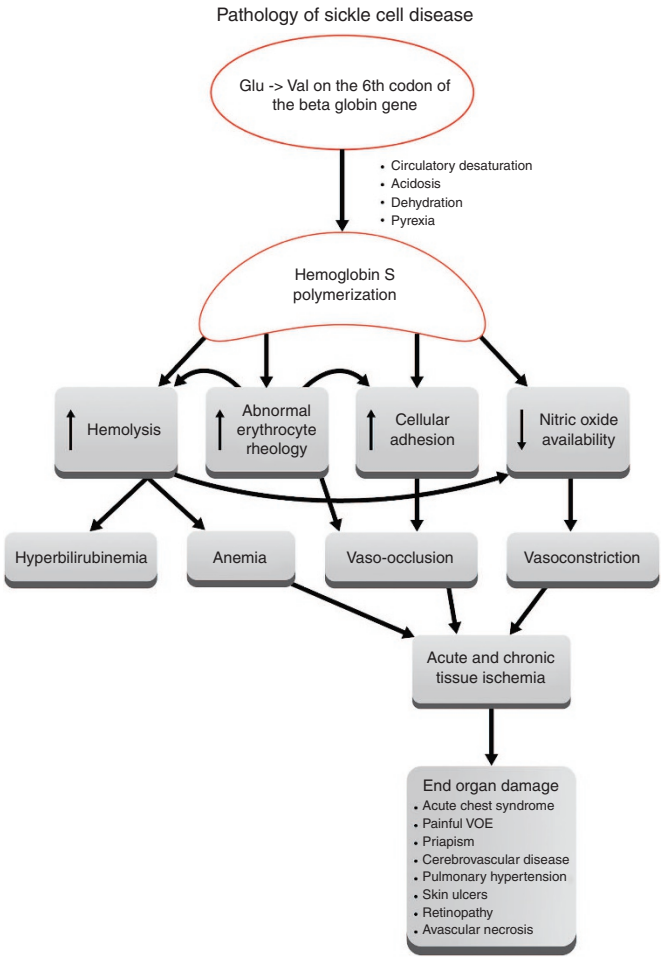

Figure 1. Sickle cell pathophysiology. The pathophysiology of sickle cell disease is complex and stems from the polymerization of HbS that occurs during periods of hypoxemia, dehydration, acidosis, and pyrexia. Polymers of sickle hemoglobin cause the characteristic shape change of the erythrocyte and lead to hemolysis, abnormal rheology, cellular adhesion and decreased nitric oxide availability. These changes result in anemia, vaso-occlusion and vasoconstriction that are the cause of SCD-associated end organ damage.

Dactylitis is often the first manifestation of SCD and can occur as early as 6 mo of age (40). In older children and adults, musculoskeletal pain is the most common complaint. Patients with SCD can have chronic pain syndromes and additionally experience acute VOE (38). Nonpharmacologic management of VOE includes maintaining adequate hydration, application of heat to the affected area(s), relaxation, distraction, and cognitive behavioral therapy. Anti-inflammatories and opioid pain medication can initially be administered orally at home and then intravenously in a medical care facility if the pain continues. Because VOE is the most common acute complication seen in patients with SCD, studies of a number of novel therapies to treat or prevent acute VOE are ongoing or have recently concluded (**Table 2**).

Acute Chest Syndrome

Acute chest syndrome (ACS) is characterized by pulmonary infiltrate in patients with SCD accompanied by one or more of

Table 2. Novel agents for the prevention or treatment of acute vaso-occlusive episodes

Agent	Mechanism of action	Prior trial outcomes	Current trials/Clinical Trials.gov Identifier
Rivipansel (GMI 1070)	Pan selectin inhibitor that prevents cellular adhesion between erythrocytes, leukocytes, platelets, and vascular endothelium.	Phase II trials showed reduced time to VOE resolution and amount of iv opioid dispensation for acute VOE in children and adults with SCD (87)	Phase III trial of Rivipansel for treatment of acute VOE in adult and pediatric patients (NCT 02187003)
Poloxamer 188 (MST 188)	Stabilizes damaged cell membranes, impairs cellular adhesion, improves rheology of sickled red cells.	Prior aggregate analyses of children and adults did not show differences between treatment and placebo groups for time to VOE or amount of opioid needed to treat VOE. Subanalysis of children under age 15 y however showed beneficial effects with and without hydroxyurea use (88)	Phase III trial of Poloxamer 188 for acute VOE is continuing to recruit adult and pediatric patients (NCT01737814)
Prasugrel	Inhibitor of the $P2Y_{12}$ ADP platelet receptors resulting in inhibition of platelet activation and aggregation.	Pediatric trial failed to show reduction in rate of VOE managed at home, VOE requiring hospital care or rate of ACS.	Completed, data published in February 2016 (89)
AES-103 (5-hydroxymethyl Furfural)	Maintains HbS molecule in conformation that does not undergo polymerization.	Phase I clinical trials in volunteers and persons with SCD	Phase II placebo controlled trial in adult and pediatric patients at two dose levels terminated.
HQK-1001	Butyrate compound which increases HbF production.	Double blinded placebo controlled trial in adults and children 12 y and older	Phase II trial stopped early after a planned interim analysis failed to show improvement in HbF and the HQK-1001 group also showed trend to increased VOEs (90)
Regadenoson	Adenosine A2A agonist which reduces levels of invariant natural killer T (iNKT) cells whose activation has been implicated in VOEs.	Phase I trial showed safety of dosing in adults and children in both steady state and during VOE (91)	Adult and Pediatric Phase II trial in progress for acute VOE (NCT01788631)
Magnesium	Known vaso-dilator, anti-inflammatory and pain reliever.	Double blinded placebo controlled trial of Magnesium vs. normal saline in pediatric patients with SCA to determine if Magnesium would decrease length of VOE and iv opioid use.	Intravenous Magnesium did not significantly reduce the length of VOE or iv opioid use compared to placebo (92)
Omga-3 docosahexaenoic acid (DHA)	Low omega-3 fatty acid levels are a contributor to increased erythrocyte adhesion, aggregation, and inflammatory mechanisms that are important in the pathophysiology of VOE.	Omega-3 fatty acid supplementation decreased the rate of VOE in a single center.	Phase III study in children ages 5–17 y planned, but not yet recruiting. (NCT02604368)
Arginine	Low plasma arginine levels were predictive of admission for VOE	One dose of arginine increases nitric oxide (NO) in patients with SCD.	Phase II study of iv arginine therapy for acute VOE is recruiting patients between the ages of 3 and 21 y (NCT 02536170)
		Children who were admitted with VOE and received oral arginine had more than 50% reduction in parenteral opioid compared to the placebo group. Length of stay did not differ between the treatment and placebo group.	

SCD, sickle cell disease; VOE, vaso-occlusive episodes.

the following: chest pain, cough, fever, hypoxia, wheezing, or tachypnea (41). ACS may be the result of sickling in the microvasculature causing pulmonary infarction/emboli or viral or bacterial pneumonia. ACS may develop as an isolated event, or during the course of a VOE often in relation to sedation, hypoventilation and fluid overload (41). ACS is the leading cause of death in SCD patients and the second most common cause for hospitalization (5). Incidence increases in patients with a history of asthma or prior ACS (42).

Since it is nearly impossible to differentiate ACS caused by infection from ACS caused by infarction, antibiotic therapy should be initiated with a cephalosporin and a macrolide antibiotic for coverage of atypical organisms in all patients with ACS. Aggressive use of incentive spirometry can help to minimize progression of ACS. Bronchodilators are commonly used in people with a history of asthma and with evidence of acute wheezing, although randomized controlled trials of this modality have not been performed. While 61% of patients in the National Acute Chest Syndrome Study had been treated with bronchodilator therapy, only 20% achieved clinical improvement (defined in this study as a 15% increase in the Forced Expiratory Volume in 1 s (FEV1)) (41). Hyperhydration

should be avoided as it can lead to pulmonary edema and worsening respiratory status (43). Depending on the severity of ACS and level of hypoxia, positive pressure ventilation in an intensive care setting may be needed (44). Simple transfusion may be used if the baseline hemoglobin is low and the patient is hypoxemic, while exchange transfusion may be indicated for more severe ACS (multi-lobar involvement, progressive respiratory depression, and/or respiratory failure) (44).

Cerebrovascular Disease

Stroke is defined as an acute neurological syndrome caused by occlusion of an artery or a hemorrhage with resultant ischemia and neurological signs and symptoms lasting more than 24 h. Prior to routine TCD screening, approximately 10% of children with SCA under age 20 suffered a stroke (35). The incidence is highest between ages 2 and 9 y (45). In general, the incidence of hemorrhagic stroke peaks in the third and fourth decades of life while cerebral infarctions occur in younger groups as well as after age 50 y (45). The etiology of vascular occlusion in SCD is likely a combination of accumulated sickled erythrocytes in the microvasculature and vascular intimal hyperplasia. Vascular intimal hyperplasia and thrombosis may be related to the abnormal adhesive and procoagulant properties of erythrocytes containing HbS. Altered vascular reactivity manifested as inability to develop compensatory vasodilatation and vasospasm may also be contributing factors. Children who have experienced a stroke are managed with chronic transfusion therapy to maintain HbS levels of < 30% (46–48). This significantly reduces but does not eliminate the risk of repeated stroke. Chronic transfusion therapy ultimately causes transfusional iron overload which requires iron chelation therapy.

Over 35% of children with SCA have evidence of "silent" infarcts (49). Since the mid-1980's studies have shown that some children with SCD may experience subtle neuropsychological abnormalities thought to be related to silent cerebral infarction (SCI). The recently published Silent Infarct Transfusion Trial (SIT trial), a randomized trial that compared monthly transfusions to observation (the standard of care at the time the study was initiated) confirmed significant neurocognitive deficits in children who had SCI compared to controls with SCA but without SCI (50). SCI was defined by the SIT investigators as an abnormal MRI signal that was at least 3 mm in size and visible in two planes in a child with SCA who had either a normal neurologic exam or an abnormal neurologic exam that could not be explained by the location of the lesion (or lesions) seen on the MRI (50). Most SCIs occur in the deep white matter of the frontal lobes and 60% are bilateral. The SIT trial showed that transfusions significantly decreased the composite end point of neurologic events which included overt strokes, transient ischemic events and SCI. While the SIT trial suggests that children with SCI should receive monthly transfusions to maintain HbS levels less than 30%, the benefits of transfusion therapy must be balanced with the risks of transfusional hematochromatosis, the availability of phenotypically matched blood, the risks of alloimmunization, and the risks of sedation to obtain brain MRI/MRA needed to detect SCI. While observation was the standard of care at the time the SIT trial was initiated, the current standard of care for children with SCA is hydroxyurea therapy beginning at age 9 mo (11). The effect of hydroxyurea on the incidence of SCI is unknown, but is the focus of the ongoing HUPrevent trial (NCT01389024).

Priapism

Priapism is a distressing complication of prolonged, unwanted, painful penile erection reported by 35% of males with SCD (51). The mechanistic causes of priapism are multi-factorial and include polymerization of HbS and erythrocyte sickling within penile venules which prevents blood from escaping the corpus cavernosum, increased adhesion of the sickled erythrocytes to the penile vasculature, as well as decreased nitric oxide (NO) availability caused by increased uptake by free plasma hemoglobin and decreased production by the penile endothelial tissue (51–53). Episodes that are multiple and self-limited to less than 4 h are referred to as stuttering priapism. Prolonged, untreated episodes are associated with a high incidence of impotence related to fibrosis of tissue (54).

Randomized clinical trials are lacking and therapeutic options for priapism are limited. The mainstay of pharmacologic treatment are alpha and beta adrenergic agonists which induce smooth muscle relaxation. A comparison of daily alpha adrenergic agonist therapy (either short acting etilefrine or longer acting pseudoephedrine) to placebo found no significant differences in the frequency of stuttering priapism attacks or the level of pain accompanying the episodes of priapism between the groups (51). Intracavernosal injections of either of these alpha agonists is more efficacious and is considered the standard of care for SCD-associated priapism (54,55). Terbutaline, a beta adrenergic agonist, has been used to treat pharmacologic-induced priapism, but has not been studied as a treatment for SCD-associated priapism (54). A small double-blind, placebo-controlled randomized trial of sildenafil (a phosphodiesterase 5 inhibitor) did not find a significant difference in the number of priapism episodes between the sildenafil and placebo groups. However, when open-label sildenafil was offered to participants after study conclusion, 7 of the original 13 participants who continued sildenafil reported a decreased frequency of priapism (56).

DISEASE-MODIFYING THERAPIES AND CURATIVE OPTIONS

Hydroxyurea

Fetal hemoglobin (HbF) contains two α chains and two γ globin chains. In healthy infants, HbF production is silenced postnatally and hemoglobin A (HbA) becomes the predominant hemoglobin (57). In infants with SCD, however, HbF is replaced by HbS instead of HbA during the postnatal hemoglobin switch. Children and adults whose erythrocytes still contain a high concentration of HbF have a milder clinical SCD course than those who have low intraerythrocytic HbF concentrations. Hydroxyurea (HU), a once daily oral medication, increases HbF levels by inhibiting ribonucleotide reductase (58). HbF decreases intraerythrocytic HbS concentration

and prevents HbS polymerization, thereby decreasing erythrocyte sickling and subsequent hemolysis (59). Additional mechanisms of HU action include reduction in neutrophil and platelet count, thereby ameliorating the abnormal cell adhesion-inflammation pathways as well as correcting the nitric oxide deficiency state brought about by SCD-associated hemolysis (60–62). The Multi-Center Study of Hydroxyurea was a multicenter, randomized, double blind, placebo-controlled trial to determine if daily HU could decrease the frequency of painful VOEs in adults with SCA; HU treatment resulted in a 44% reduction in the rate of VOE (63). Fewer patients assigned to the HU treatment arm experienced ACS, and fewer needed transfusion (63). Similar studies have been conducted in pediatric patients with SCA, with the youngest enrollment age being 9 mo in the BABYHUG (multi-center randomized, placebo-controlled trial of HU in young children with SCA) and all had results that were similar to the initial Multi-Center Study of Hydroxyurea study with decreased VOC, ACS, and transfusions in the HU group (64–66). Importantly, the growth, development or risk of genotoxicity did not differ between the two groups in the BABYHUG study (64,67,68). The children who participated in the original BABYHUG study are entering adolescence, and their growth, development and organ function continues to be monitored through the BABYHUG 2 follow-up study (NCT 01783990). However, given the safety profile generated from the BABYHUG data and the significant decrease in clinical events, the 2014 NHLBI Evidence Based Management Guidelines for Sickle Cell Disease recommends that all infants 9 mo of age and older with SCA be offered HU as treatment, regardless of the frequency or severity of disease complications (11).

Two recent studies have compared the efficacy of HU and phlebotomy (alternate treatment) to transfusions with chelation (standard treatment) for primary or secondary stroke prevention. The study of secondary stroke prevention, SWiTCH (Stroke With Transfusion Changing to Hydroxyurea), was stopped early by the study's Data Safety Monitoring Board when a scheduled interim analysis revealed statistical futility for reaching the composite primary endpoint of both recurrent stroke rate and improved transfusional hematochromatosis. The SWiTCH study design allowed for an increased rate of stroke in the alternate treatment (HU + phlebotomy) group provided that iron burden was improved because of the significant organ damage that transfusional hematochromatosis can cause. The stroke rate in the alternative arm was higher than the standard treatment arm as expected, but phlebotomy was inferior to chelation at improving iron overload, so the composite endpoint was not reached. Due to the inferior results on SWiTCH's hydroxyurea/phlebotomy arm, chronic transfusion plus chelation remains the mainstay of secondary stroke prevention in children with SCA (69).

HU and phlebotomy was recently found to be an acceptable alternative to standard treatment (transfusion/chelation therapy) for primary stroke prevention in children with abnormal TCD velocities without evidence of severe vasculopathy on brain MRI/MRA (70). Small cohort studies indicated that HU may reduce TCD velocities from abnormal or conditional to normal (71,72). The TWiTCH study randomized children with abnormal TCDs who had received at least 1 y of chronic transfusion therapy but without severe cerebral vasculopathy (70) to either continue transfusion therapy and iron chelation with deferasirox or change to HU and phlebotomy. In the alternate treatment arm, transfusions were weaned over 4–9 mo as HU doses were escalated to maximum tolerated dose, based on absolute neutrophil count. Phlebotomy commenced once transfusions had stopped, and patients were monitored by TCD every 3 mo to ensure that TCD velocities did not revert to abnormal. The first scheduled interim analysis showed noninferiority of the alternative therapy arm. After 50% of participants had exited the study, repeat analyses supported these findings and the study was terminated by the NHLBI (37). These findings support HU and phlebotomy as an acceptable substitute for standard treatment in children with abnormal TCD but without severe vasculopathy who have received at least 1 y of chronic transfusion therapy.

HU use has been extended to patients who have hemoglobinopathies other than SCA, such as HbSC or HbSβ^+ thalassemia with frequent VOE or recurrent ACS. However, their responses to HU are extremely variable and there is also considerable variation in the dose of drug that individual patients are able to tolerate, some experience myelotoxicity at only 7.5 mg/kg/d and others are able to take up to 30 mg/kg/d (73).

Transfusion Therapy

Blood transfusions are used for management of acute conditions and prevention of complications associated with SCD (74). Methods of transfusion depend upon the underlying goal of therapy. Sickled erythrocytes are intrinsically more rigid and viscous therefore substantially raising the hematocrit without first reducing the proportion of sickled cells can lead to dangerous levels of blood viscosity. For this reason, simple transfusions must be used with caution for patients with hematocrit ≥25%. Since the main transfusion goal in patients with SCD is reducing the HbS concentration, patients with SCD should only receive sickle negative pRBCS (74). Nearly one third of patients with SCD will develop alloantibodies with standard ABO and Rh matched pRBCs (75). Limited phenotyping for C, E, and Kell should be performed for all patients with SCD and extended antigenically matched pRBCs should be provided for patients with known alloantibodies to less frequently occurring antigens (like Duffy or Kidd) (76,77). The list of acute complications for which transfusion is indicated is short and includes: overt stroke (exchange transfusion is superior to simple transfusion for overt stroke (78)), symptomatic severe ACS (typically with persistent hypoxia despite supplemental oxygen, worsening respiratory distress, progressive disease on chest Xray), splenic sequestration, and symptomatic acute anemia (11). Current indications listed in the 2014 NHLBI Evidence Based Management SCD Guidelines for chronic transfusion therapy include overt stroke and abnormal TCD (11).

Hematopoietic Stem Cell Transplantation

The only currently available cure for SCD is hematopoietic stem cell transplant (HSCT). Matched sibling donor transplants in patients with SCD have the highest overall survival (OS) rates (>90%), disease-free survival (DFS) rates (82–100%) and lowest rates of graft rejection (8–18%), and graft-versus-host disease (GVHD) (6–35%) (79). Myeloablative conditioning regimens are associated with end organ toxicities, including gonadal toxicities that frequently result in sterility, a concern for patients and families (80,81). Reduced intensity condition regimens for matched sibling donor HSCT have recently been shown to have similar rates of OS (93%), DFS (90.7%), and GVHD (23% acute GVHD, 13% chronic GVHD) (82). Unfortunately, less than 20% of patients with SCD have a matched sibling donor (83).

Studies evaluating alternative donor HSCT utilizing stem cells from matched unrelated donors or haploidentical donors are ongoing and have shown mixed results. Haploidentical HSCT have low rates of GVHD, but high rates (40–50%) of graft rejection (84). Conversely, matched unrelated donor HSCT have relatively low rates of rejection, but higher rates of GVHD (85,86). The SCURT trial (unrelated donor reduced intensity bone marrow transplant for children with severe SCD, NCT00745420) has completed enrollment, but data accrual and analysis is ongoing. The umbilical cord arm of the study was closed early due to high rates of graft rejection which met the pre-determined stopping rule (85). STRIDE (A Study to Compare Bone Marrow Transplantation to Standard Care in Adolescents and Young Adults with Severe SCD, BMTCTN#1503, NCT02766465) will evaluate MUD HSCT in patients with SCD between the ages of 15–40 y. Eligibility for HSCT trials generally includes severe SCD which is defined as one or more of the following SCD-associated complications: overt stroke, abnormal TCD, recurrent ACS or severe VOE despite appropriate supportive care, red cell alloimmunization with an established indication for chronic transfusion therapy, pulmonary hypertension, recurrent priapism, sickle nephropathy or bone and join involvement (79). Eligibility for ongoing HSCT trials to patients who do not meet these inclusion criteria is a source of ongoing discussion among hematologists, bone marrow transplant physicians and medical ethicists, given what is known about the early mortality in patients with SCD and decreased quality of life (6,87,88).

Patients with SCD undergoing HSCT are at higher risk for intratransplant complications than other nonmalignant HSCT candidates, particularly intracranial hemorrhage. Aggressive supportive care with erythrocyte and platelet transfusions is necessary and transfusion thresholds are higher for patients with SCD than other HSCT patients (89). Additionally, avoidance of hypertension and hypomagnesemia are especially important to avoid neurologic sequelae in the immediate post-HSCT period (90). The risks and benefits of HSCT should be carefully considered for each sickle cell patient. Referral to transplant centers with experience in performing HSCT for sickle cell patients is imperative given the increased level of supportive care needed by this population.

Gene Therapy

SCD is an excellent candidate for gene modifying or replacement therapies because it is monogenetic and the causative point mutation has been well studied and characterized over the past half century. Since fewer than 20% of people with SCD will have a matched sibling donor for HSCT, gene therapy is an attractive curative option. Gene therapy strategies include replacing the defective β-globin gene utilizing viral vectors, inserting gamma globin genes (thus augmenting HbF production), and genome editing to reactivate silenced gamma globin genes (91–93). Successful gene therapy requires safe and efficient gene transfer to the hematopoietic stem cell population and thereafter stable long term gene expression. Human trials in patients with β-thalassemia major are further advanced than in patients with SCD and have shown success. Trials that are actively recruiting SCD patients include those utilizing a γ-globin expressing vector (NCT02186418), a triple β-globin mutant, β-AS-3, which has increased affinity for α-globin subunits (NCT02247843), and a vector that expresses a non-sickling β-globin mutation, T87Q (NCT02151526 and NCT02140554). Two comprehensive reviews on gene therapy in SCD provide more in depth information (92,93).

Novel Agents for Management or Prevention of Acute Complications

Novel approaches to treatment, both for acute complications of SCD as well as disease modifying therapy, are currently under investigation and have been recently described in a comprehensive review (94). Phase II or III trials of compounds to either prevent or treat acute VOEs in children with SCD are described in **Table 2** (95–100).

TRANSITION FROM PEDIATRIC TO ADULT CARE SYSTEMS

Transition from pediatric to adult hematology care is often fragmented and abrupt in adolescents and young adults (AYA) with SCD (101). AYAs with SCD around the time of transition have increased emergency department utilization for acute complications, increased readmission rate, and increased mortality (4,10,102). In addition to novel and curative therapies, quality improvement and clinical trials should be focused on assessing transition readiness and improving AYA transition to the adult care system as well as best ways to partner with adult providers to decrease patient and family anxiety about leaving pediatric practices, financial and insurance burdens of chronic diseases, and improving AYA responsibility for their own healthcare (103–105).

The 2014 NHLBI guidelines contain consensus statements regarding the reproductive counselling of men and women with SCD as well as US Preventive Services Task Force-aligned recommendations for the pregnant woman, with special emphasis on the effects of maternal alloimmunization and use of opioid pain medications on the fetus (11). Contraceptive therapy can provide health benefits to women with SCD by minimizing menstrual blood loss and decreasing the rate of VOE during the menstrual cycle (106). The Center for Disease Control's Medical Eligibility Criteria for Contraceptive Use provide safe contraceptive therapy choices for women with SCD (107).

CONCLUSIONS

SCD has been a recognized condition for over a century. Despite this fact, early mortality is the norm and morbidity from disease complications commonly affects quality of life. The three mainstays of therapy are HU, blood transfusion and HSCT, but many new therapeutic options are under investigation as well as opportunities for care improvement, giving patients, families, and medical care providers reason for hope that early mortality from SCD will improve.

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