Chapter 3
Current Non-HSCT Treatments for SCD

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Sickle cell disease (SCD) is characterized by episodes of acute complications and ongoing chronic organ disease which has been associated with significant morbidity and premature death. Advances in health care along with public health measures have led to significant reduction in mortality for children with SCD, at least in developed countries. Universal newborn screening, penicillin prophylaxis, vaccinations, and hydroxyurea (HU) therapy, along with transcranial Doppler for stroke screening and use of chronic transfusion, have successfully changed SCD from a life-threatening disease to a chronic condition. The majority of patients now survive into adulthood requiring lifelong comprehensive care.

Management of SCD has been largely supportive until recently. The use of disease-modifying therapies such as HU and chronic blood transfusions is expanding, and hematopoietic stem cell transplant (HSCT) is also becoming increasing available as a potential curative therapy for SCD. This chapter will primarily focus on HU in addition to reviewing supportive care for SCD and emerging therapies. Chronic transfusions and HSCT are discussed briefly as these topics are being reviewed in chapters focused on these specific areas.

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Disease-Modifying Therapies

Hydroxyurea

Hydroxyurea (hydroxycarbamide, HU) is a FDA-approved disease-modifying therapy for SCD. Until recently, HU was primarily prescribed to individuals with severe disease who experienced complications such as recurrent vaso-occlusive painful episodes and acute chest syndrome. However recent National Heart, Lung, and Blood Institute (NHLBI) practice guidelines strongly endorse HU and suggest offering it to patients with sickle cell anemia (SCA) from 9 months of age regardless of clinical severity [1]. While the majority of evidence supporting HU use comes from SCA, HU is also considered in patients with HbSC and HbSβ^+ thalassemia who have severe disease as indicated by frequent pain or other complications of SCD [2, 3].

HU is an old drug first synthesized in 1869 by Dresler and Stein, although its clinical application was not until a century later for treatment of various myeloproliferative disorders. Clinical observations from the initial cohort studies had documented the beneficial effects of fetal hemoglobin (HbF) in SCD prompting investigation of the induction of HbF in patients with SCD [4]. In the 1980s the effect of HU as an HbF-inducing agent in SCA was published [5]. Subsequently, studies conducted to determine if the laboratory effects of HU would translate into clinical benefits showed that increased HbF was associated with improved outcomes in SCA. It is however becoming clear that induction of HbF is not the only mechanism that underlies the beneficial effects of HU in SCD.

Several cell cycle-specific agents are known to have the ability to induce HbF production, some of which have been tried in SCD [6]. Given other convenient properties such as rapid absorption, high bioavailability, oral formulation, and once-daily dosing, the clinical application of HU in SCD became of interest, and Platt et al. pioneered its use in SCD [5]. HU, a monohydroxyl-substituted urea (hydroxycarbamate) antimetabolite, selectively inhibits ribonucleotide diphosphate reductase, an enzyme required to convert ribonucleoside diphosphates into deoxyribonucleoside diphosphates, thereby preventing cells from leaving the G1/S phase of the cell cycle [7]. Reversible inhibition of ribonucleotide reductase and resulting inhibition of progression of cellular division and temporary arrest of hematopoiesis lead to altered erythroid kinetics by recruitment of early erythroid progenitors that maintain their HbF-producing capability [8]. Another mechanism postulated for increased HbF suggests that HU may act directly on the late erythroid precursors to produce HbF or may alter the transcription factors that modulate globin gene enhancers [9, 10]. Nitric oxide-dependent activation of soluble guanylyl cyclase has also been proposed to play a role in HU-induced HbF production [11]. Increased HbF concentration leads to reduction in polymerization of sickle hemoglobin (HbS) and sickling of red blood cells. Red blood cells with high HbF are larger, less dense, and more deformable, thus exhibiting improved rheology [12]. HU also affects myelopoiesis leading to dose-dependent leukopenia, neutropenia,

and thrombocytopenia. Additionally, its use has been shown to be associated with reduction in chronic inflammation and increased levels of nitric oxide that may improve vascular tone and reduce expression of surface molecules that adhere to endothelium. [11, 13, 14].

The multicenter study of HU (MSH) was a double-blind placebo-controlled trial in adults with SCA which was designed to test the efficacy of HU in reducing the frequency of painful crises. A report of three or more pain crises in a year was needed to meet the study entry criteria. The study showed that HU reduced the frequency of hospitalization for pain, acute chest syndrome, and need for blood transfusion [15]. The trial was stopped prior to its planned 2-year duration due to the observed beneficial effects of HU. These clinical benefits of HU were also associated with beneficial laboratory findings which included increase in hemoglobin concentration and HbF levels and reductions in neutrophil count and markers of hemolysis. In addition, a later follow-up study of MSH participants showed prolonged survival in patients treated with HU [16]. HU was approved for use in symptomatic SCD by the FDA in 1998. Although the approval did not extend to pediatric patients, comparable studies in children have confirmed that HU is safe, efficacious, and well tolerated [17–19]. Due to the favorable effects of HU observed in adults and children with SCD, it was hypothesized that early institution of HU could reduce or prevent damage to organs especially the brain, spleen, and kidneys. This hypothesis led to the phase III randomized double-blind placebo-controlled trial (BABY HUG) conducted in 9–18-month-old children with SCA. Unlike the MSH trial, meeting of disease severity criteria was not needed for the study entry. At the end of the study, while the primary end point of preventing organ damage was not met, HU was effective in reducing the number of episodes of dactylitis and other vaso-occlusive episodes, number of hospitalizations, and need for transfusions [20]. Benefits of HU extend beyond the outcomes evaluated on initial studies. Data is emerging suggesting efficacy of HU in preventing end-organ damage. HU has been shown to be effective in children with conditional transcranial Doppler velocities, as an alternative to transfusion in non-transfusable patients, and to delay the onset of end-stage renal disease in patients with nephropathy [21–23]. Additionally, long-term use of HU may improve survival in patients with SCD [16, 24].

Stroke is a devastating complication of SCD. Until recently blood transfusion was the only treatment available for prevention of stroke in this population. Many recent studies have evaluated the effect on HU on SCA-associated stroke. The Stroke with Transfusions Changing to HU (SWiTCH) trial was a multicenter phase III randomized open-label, non-inferiority trial designed to compare standard treatment (transfusions and chelation) to alternative treatment (HU at maximum tolerated dose and monthly phlebotomy) for reduction of secondary stroke and management of iron overload [25]. The study population included children with SCA and previous stroke who had been on chronic transfusions for 18 months or more with iron overload. The composite primary end point of the study included recurrence of stroke and iron overload. Results of interim analysis showed no recurrence of strokes in subjects on transfusions/chelation arm compared to 7 (10%) on HU/phlebotomy arm. Although this difference in stroke recurrence was still in the non-inferiority

range (12%), liver iron content was equivalent in the groups. Given these results the study was closed early. It was concluded that in children with SCA, stroke, and iron overload, current approach of transfusions and chelation is superior to HU and phlebotomy for secondary stroke prevention [25]. Recently the outcomes for TCD with transfusions changing to HU (TWiTCH) trial have been published [26]. This was a multicenter, phase III, randomized, open-label, non-inferiority trial that enrolled 121 participants aged 4–16 years with SCA on chronic transfusions with abnormal TCD $\geq$ 200 cm/s but no severe vasculopathy who had received at least 12 months of red cell transfusions. Patients were randomly assigned to continue transfusions (standard group $n = 61$) or transition to HU (alternative group $n = 60$). The study was terminated early as the first interim analysis showed non-inferiority of HU to ongoing transfusions. It was concluded that children with SCA with abnormal TCD velocities on chronic transfusions for a least 1 year with no MRA-defined severe vasculopathy can be switched to HU for primary stroke prevention [26].

HU is a myelosuppressive agent so it is recommended that a protocol for monitoring should be followed to ensure patients are receiving an adequate dose without evidence of myelotoxicity. The NHLBI published evidence-based guidelines providing a consensus treatment protocol for the implementation of HU therapy [1]. The effect of HU is dose dependent, and studies indicate that reaching maximum tolerated dose (MTD) may be beneficial in SCD [19, 21]. Prior to starting HU, baseline studies should be obtained including complete blood count (CBC) with differential, reticulocyte count; platelet count; RBC mean corpuscular volume (MCV); quantitative measurement of HbF if available; comprehensive metabolic profile, including renal and liver function tests; and pregnancy test if appropriate. These parameters should be followed periodically as described in the NHLBI guidelines and summarized below [1]. During monitoring visits, providers should elicit symptoms of toxicity and reiterate adherence, advising patients not to take extra doses if a dose is missed and to continue to take HU when sick or hospitalized unless instructed by a physician. Contraceptive counseling prior to HU initiation and at follow-up visits should also be provided to patients of both genders.

The usual starting dose for infants and children is 20 mg/kg/day and a lower dose of 15 mg/kg/day for adults with SCD. For patients with concomitant chronic renal disease, starting dose should be lowered to 5–10 mg/kg/day. Patients should be monitored with CBC with differential and reticulocyte counts every 4 weeks during dose escalation which is typically done in increments of 5 mg/kg/day every 8 weeks to a maximum dose of 35 mg/kg/day. Adult dose typically is 1500–2000 mg daily. The goal absolute neutrophil count (ANC) is >2000 μL^{-1}; however children with lower baseline ANC may safely tolerate counts down to 1250 μL^{-1}. HU is held for significant cytopenias of ANC < 1000 μL^{-1}, platelet count <80,000 μL^{-1}, or reticulocyte count <100 K/μL (unless hemoglobin >8.0 g/dL). CBC with differential and reticulocyte counts is monitored weekly till count recovery following which HU can be resumed at a dose 5 mg/kg/day lower than prior to the onset of cytopenias. Once a patient is on a stable dose, CBC with differential and reticulocyte count can be monitored every 2–3 months, and HU is continued long term. Liver and kidney function tests as well as a hemoglobin electrophoresis should be obtained every

3–6 months [2]. RBC MCV and HbF levels provide evidence of consistent or progressive laboratory response; however a lack of increase in MCV and/or HbF is not an indication to discontinue therapy. A clinical response to treatment with HU can take 3–6 months. Therefore, a 6-month trial of HU on the maximum tolerated dose is recommended prior to considering discontinuation of HU. Although poor adherence is the most common cause of treatment failure, a proportion of patients are biologically resistant to HU [27].

HU is generally well tolerated with very few reversible side effects. The most common and anticipated short-term side effect is reversible myelosuppression, leading to neutropenia, reticulocytopenia, and thrombocytopenia [27, 28]. Patients should be counseled regarding integumentary effects of skin or mucosal hyperpigmentation, melanonychia (darkening of nails), and less commonly hair thinning/alopecia [28, 29]. Mild gastrointestinal upset can also occur [28]. HU is renally excreted and small elevations in creatinine may be observed [27]. Long-term side effects are rare but may become pertinent with improved survival in SCD. Despite initial concern about effect on growth based on murine studies, no significant change in growth velocity has been reported in children taking HU [17, 20, 29–31]. There is a theoretical increased risk of malignancy with HU; however available data does not support an association between HU use in SCD and leukemia [19, 20, 29, 32]. The negative impact of HU on reproductive health is unconfirmed. A transgenic sickle cell mouse model revealed that HU treatment exacerbated SCD-induced hypogonadism to gonadal failure [33]. Small retrospective cohort studies have revealed sperm abnormalities in males with SCD which are exacerbated by HU [34, 35]. While reproductive issues and HU are an area of future research, current recommendations suggest that patients should be counseled on the risks of HU. Sexually active couples are recommended to use contraception if one person is on HU and individuals trying to conceive should stop HU 3–6 months before discontinuing contraception [27]. Nonetheless, literature documents males and females taking HU who have given birth to healthy offspring. During the MSH study, despite mandated use of contraception for study inclusion, several successful pregnancies occurred in women taking HU and in the partners of male participants [36]. A number of cohort studies and case reports also document healthy pregnancy outcomes in women taking HU [29, 37, 38]. It is known that HU crosses the placenta and is excreted in breast milk [39]. It is recommended that HU be discontinued in pregnant and lactating women due to a lack of human data on its potential teratogenic effects [3] and with animal studies documenting reproductive toxicities of HU [40–43].

Despite the substantial body of evidence in favor of HU, this medication remains underutilized [28]. Barriers to use are many and exist at the provider, patient/parent, and systems levels [44]. Provider surveys have uncovered a lack of awareness and varying interpretation of the risk versus benefits of HU [45] and perceived patient apprehension about adverse effects, treatment adherence, and compliance with contraception [46, 47], and burdens of laboratory monitoring [47] contribute to underutilization of HU. Parental survey revealed factors such as that HU was not always being offered by hematologists and also concerns for side effects related to HU use in particular efficacy, long-term safety, and off-label use affect HU use [48].

System-related barriers including issues surrounding health disparities also play a role. For patients on HU, ongoing medical monitoring for toxicities is vital. The need for frequent visits may present monetary challenges for the families belonging to disadvantaged populations that may have poorer access to transportation, coordinated health care, and health insurance which in turn may lead to underutilization of HU [44]. Nonetheless, HU has been shown to result in significantly lower overall estimated medical care costs. Data from the BABY HUG study compared cost of medical care in children taking HU to those on placebo. The study revealed that while estimated outpatient expenses were increased in the HU group, the number of hospitalizations was lower resulting in overall lower cost for SCD children on HU. The total annual estimated cost was 21% lower in the HU group ($11,072) compared to those on placebo ($13, 962: $P = 0.038$) [49].

SCD is a global disease due to the fact that HbS trait bestows a survival advantage from malaria [50]. The burden of SCD is increasing particularly in Africa; it was estimated in 2010 that 79% of children with SCD were born in sub-Saharan Africa, projected to increase to 88% by 2050 [51]. Africa and other low-income countries worldwide are resource-limited with immense disparities in management and health outcomes in SCD compared to high-resource countries [52]. Due to its efficacy, low cost, and ease of administration, HU is an ideal drug for low-resource countries. HU is safe and of proven benefit in resource-rich settings; whether this translates to low-income settings remains to be established [53, 54]. Studies evaluating the safety, sustainability, and efficacy in these low-resource settings challenged with comorbidities such as malaria, HIV, and severe malnutrition are imperative [28]. Several studies are ongoing to bridge this knowledge gap. The Realizing Effectiveness Across Continents with HU (REACH, ClinicalTrials.gov NCT01966731) trial is a multicenter prospective phase I/II open-label, dose escalation study of HU. The study plans to recruit a total of 600 children age 1–10 years with SCA in sub-Saharan Africa. The study will evaluate feasibility, safety, and benefits of HU. The Novel use of HU in an African Region with Malaria (NOHARM, NCT01976416) is a prospective randomized, placebo-controlled, double-blind phase III trial that seeks to identify hematologic toxicities, adverse events, and risk of malaria with low fixed-dose oral HU versus placebo. It will also establish correlations between HU treatment and fetal hemoglobin, soluble intracellular adhesion molecule-1, and nitric oxide levels and between levels of these biomarkers and risk of malaria. This study aims to recruit 200 Ugandan children aged 1.00–3.99 years with SCA [53]. Primary stroke prevention is a priority in the care of patients with sickle cell. The Primary Stroke Prevention in Nigerian Children (SPIN, NCT01801423) study is a NIH-sponsored SCD clinical trial in sub-Saharan Africa [55]. This is a single-site, single-arm pilot trial in which children ages 5–12 years with elevated TCD measurements >200 cm/s in the middle cerebral artery will receive low fixed-dose HU (approximately 20 mg/kg) and will be monitored for adherence and adverse events. Preliminary data is promising with 10 out of 11 patients within 3 months showing reduced middle cerebral artery velocities below 200 cm/s [55]. If these studies show HU is safe and beneficial in resource-limited settings, this could transform the care of children with SCA in Africa.

Blood Transfusions

Red blood cell transfusions are a mainstay treatment for SCD. Transfusions are often used to treat or prevent some of the complications of SCD. Donor red cells contain hemoglobin A; thus transfusion of these cells lowers the percent of sickle hemoglobin-containing red blood cells and lowers the rate of SCD-related complications. Side effects include allergic reaction, delayed hemolytic transfusion reaction, alloimmunization, and iron overload. All individuals with SCD should be given leukocyte-reduced sickle-negative blood. To prevent alloimmunization, many institutions match the units for minor Rh and Kell antigens per NHLBI guidelines [1]. The most common indications for acute transfusions include complications such as stroke or acute neurological deficit, acute exacerbation of anemia, acute chest syndrome, and preoperative management. The most common indication for chronic blood transfusion includes primary or secondary prevention of stroke in SCD [56]. Details of transfusion therapy including indications and complications are reviewed in Chap. 5 (Transfusion support for SCD patients).

Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only available therapy with curative potential for SCD. Its availability has been increasing but still remains limited due to various reasons. Goals of HSCT include establishing stable donor engraftment and long-term donor-derived erythropoiesis [57]. Decision to transplant is generally weighed based on risk-benefit ratio depending on patient's status and donor availability. Details of HSCT in SCD are reviewed in the chapters dedicated to this subject in this book.

Supportive Therapies

Analgesics

Analgesics are used to treat pain associated with SCD. When possible, non-pharmacological measures should also be utilized as an adjuvant therapy for managing pain. It is important to remember that pain management is guided by patient report, and there are no biomarkers or imaging studies to assess pain at this time. Safe and effective management of pain requires ongoing assessment and individualization of therapy with combined use of pharmacologic and non-pharmacologic approaches. For appropriate age-based dosing, please refer to drug-specific package inserts and formulary resources.

Non-opioid Analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line agents for managing pain of mild to moderate intensity. NSAIDs are available in oral or parenteral preparations and are also used as an adjuvant to opioids for painful episodes of moderate to severe intensity. NSAIDs work by blocking the action of cyclooxygenase (COX) which is responsible for converting arachidonic acid to prostaglandins. While aspirin is not recommended for children due to association with Reye's syndrome, NSAIDs such as ibuprofen are commonly used [58]. Parenteral preparations of NSAIDs such as ketorolac tromethamine are often used during inpatient management of severe painful episode. The evidence supports use of NSAID in reducing pain and decreasing length of hospital stay associated with acute vaso-occlusive pain [59]. Gastric, renal, and platelet toxicities should be considered when using NSAIDs.

Acetaminophen and other para-aminophenol derivatives have analgesic and antipyretic activity but only moderate anti-inflammatory activity. These agents typically do not inhibit platelet aggregation. Care should be taken however with its use in patients with preexisting liver disease as well as those who receive large dose of acetaminophen (>4000 mg/day), and they can experience severe hepatotoxicity. Many preparations of acetaminophen are available in combination with opioids such as codeine and oxycodone. Care should be taken when using combinations as the risk of toxicity from acetaminophen may increase if dose is escalated to increase the opioid effect.

Opioid Analgesics

Opioids remain the mainstay of acute pain management in SCD. Opioids are available in oral, parenteral, rectal, subcutaneous, and transdermal preparations and may be available as short- or long-acting compounds. Morphine and other opioid agonists bind to opioid receptors and produce analgesia. Several RCTs and observational studies support using opioid therapy for treating acute pain associated with SCD [60–63]. Studies also support the use of around-the-clock dosing of analgesics versus intermittent administration when treating vaso-occlusive crises (VOCs) [64, 65]. Patients and parents should be counseled about the side effects including potential for dependence, abuse, and diversion.

The role of opioids in treating chronic pain associated with SCD has not been investigated. While reports from the American Pain Society (APS) suggest opioids are not effective in treating chronic non-cancer pain [66, 67], it is important to recognize that SCD patients can experience acute episode of pain on the background of chronic pain and opioids are indicated for such acute on chronic pain [68]. Patients with chronic pain or high rates of recurrent pain often require higher and more frequent dosing of opioids. These patients may benefit from working with a multidisciplinary pain management team which may include a hematologist, pain physician, and psychologist. These patients should have a pain management plan which includes a detailed written pain plan that provides guidance for dosing of analgesic agents for baseline and/or acute episodes of pain. These plans are typically based on an individual's pain and analgesic history.

Commonly used compounds in this category include codeine, morphine, oxycodone, hydromorphone, fentanyl, and methadone with morphine being the prototype of opioid analgesics. Relative potencies vary between various opioids and should be considered in the decision of opioid rotation and dose selection. Side effects include constipation, nausea, vomiting to sedation, and respiratory depression. It has been proposed that opioid-induced hyperalgesia can contribute to development of chronic pain [69]. Metabolism of opioids can be impacted by pharmacogenomics as well as the state of organ dysfunction in SCD [70, 71]. Recently FDA issued US boxed warning against using codeine in children due to the potential risk of life-threatening or fatal respiratory depression in children and adolescents [72]. This complication is related to pharmacogenomics of codeine. Codeine is primarily metabolized in the liver by the enzymes UGT2B7, CYP3A4, and CYP2D6. Ultrarapid metabolizer patients who carry two or more copies of the variant CYP2D6*2 allele have increased conversion of codeine to morphine and thus are at increased risk for opioid-mediated side effects [73]. Opioid therapy also carries the risk of tolerance, dependence, and potential for abuse; therefore patient counseling should be part of the therapy. If possible one provider should be assigned to prescribe opioids, and a treatment agreement may be considered for patients on long-term opioid therapy.

Other Adjuvant Therapies for Pain

In addition to frequently used analgesic medications above, many drugs are used to improve pain control in SCD. Most of these medications have not been tested in SCD in randomized controlled trial. Medications in this category include ketamine, dexmedetomidine, antidepressants such as amitriptyline or duloxetine, and anticonvulsants such as gabapentin and pregabalin. Ketamine is a *N*-methyl-D-aspartate (NMDA) receptor blocker and can modulate opioid tolerance and opioid-induced hyperalgesia and may be effective in managing pain in SCD [74]. Results of ketamine therapy in SCD have been mixed and are mostly based on single case report, case series, and retrospective studies data review [75, 76]. Gabapentin is often prescribed for chronic neuropathic pain and is currently being studied in SCD in a phase II study (clincialtrials.gov NCT01954927). Dexmedetomidine, an α2-adrenoreceptor agonist with sedative and analgesic properties, is used in the perioperative and intensive care settings. Dexmedetomidine has been shown to reduce opioid requirement and to facilitate opioid weaning, and its use has been reported in case series in SCD [77, 78].

Antibiotics and Immunizations

While prophylactic antibiotics and pneumococcal vaccination have reduced the incidence of invasive pneumococcal infection significantly, fever in a SCD child is still considered an emergency. Patients with SCD are at very high risk for serious

infections including bacteremia and meningitis. Due to functional hyposplenia in SCD, patients are highly susceptible to encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* [79, 80]. Frequent systemic infections with enteric organisms such as *Salmonella species* and *Staphylococcus aureus* are also seen [81]. Patients are also at risk for diverse group of organisms such as *Mycoplasma* in acute chest syndrome. Gram-negative enteric infection can involve the urinary tract, bones, and hepatobiliary system. In addition to functional asplenia, deficits of immunologic function have been reported in SCD. Innate immune system abnormalities include neutrophil dysfunction with decreased chemotaxis, migration, phagocytosis, and bactericidal properties [81] and inability to utilize the alternative pathway for C3 fixation causing defects of opsophagocytosis [82, 83]. The adaptive immune system is also impaired with a deficiency of specific circulating antibodies [83], dysfunctional IgG and IgM antibody response [84], and reduced CD4+ and CD8+ subsets in SCD patients with hyposplenia [85].

Children with SCD presenting with a fever ≥101.3 °F or 38.5 °C should be promptly evaluated in a medical facility to receive parenteral antibiotics to provide coverage for *Streptococcus pneumoniae* and other potential pathogens. Complete blood count and blood and urine culture (if urinary tract infection is suspected) should be collected. While policies on how to manage febrile children with SCD may vary between institutions, in general after initial parenteral antibiotics, patients can subsequently be managed with or without oral antibiotics in children who are 1 year or older, clinically appear well, and can be followed reliably.

Penicillin Prophylaxis

Young children with SCD are at the greatest risk for bacteremia and sepsis resulting from absent or diminished splenic function which can start as early as the first year of life [86, 87]. Risk is especially high in very young children who may lack humoral immunity against *Pneumococcus*. The risk of infection in recent years has decreased significantly due to initiation of penicillin prophylaxis early after a child is diagnosed with SCD on newborn screening and immunization against *Pneumococcus* and other capsulated organisms [88]. The dose of penicillin is 125 mg PO BID which is then increased to 250 mg PO BID after 3 years of age. Erythromycin can be used in children allergic to penicillin. These measures along with parental education about the importance of fever and need for seeking urgent medical attention have contributed to improved outcomes. Current guidelines suggest that penicillin prophylaxis can be discontinued in children with SCD at age 5 years unless they have had a splenectomy or invasive pneumococcal infection [89]. However it is important to remember that compared to general population, older children and adults with SCD are at greater risk for invasive bacterial infection and should receive urgent medical attention in case of fever or any other concern for infection.

Immunizations

Various vaccine schedules have been adopted in different countries based on available resources, local epidemiology, cost-effectiveness, and legal issues [90]. All children should be immunized in accordance with their standard national immunization program unless medically contraindicated [90]. Additional vaccines to cover for *Pneumococcus* and *Meningococcus* are recommended for children with SCD. ***The Advisory Committee on Immunization Practices (ACIP) updates the immunization schedule annually; therefore readers should refer to their latest recommendations and also guidance for catchup vaccines in children with SCD***.

Children with SCD are at greater risk of pneumococcal infection [91]. Therefore, in the USA, according to the Advisory Committee on Immunization Practices (ACIP 2016), available at https://www.cdc.gov/vaccines/schedules, four injections of pneumococcal conjugate vaccine (PCV13) should be administered before 24 months of age (starting from >6 weeks of age; generally given at 2, 4, 6, and 12–15 months). PPSV23 (23-valent pneumococcal polysaccharide vaccine) is given at 24 months of age (at least 8 weeks after the last dose of PCV), and a second PPSV23 dose is given 5 years after the first dose with a third dose at age ≥65. It should be noted that practice of PPSV23 may vary among the intuitions and some institution may elect to revaccinate the adults with SCD. Providers however should be aware and counsel patients that SCD patients may be at higher risk for developing severe inflammatory reaction at the vaccination site and severe painful episode requiring hospitalization that can occur following PPSV23 vaccination [92]. SCD children particularly before 3 years of age are at higher risk of meningitis or sepsis compared to the general population [93]. It is recommended that children with SCD should be immunized against meningitis. The licensed meningococcal conjugate ACWY vaccines include MenHibrix, Menveo, and Menactra. MenHibrix (meningococcal groups C and Y and haemophilus b), a combination vaccine, is licensed for use in infants >6 weeks old. Children should receive four doses of the meningococcal vaccine at 6 weeks to 2, 4, 6, and 12–15 months. Menveo can be used in children >8 weeks and doses should be administered at 2, 4, 6, and 12 months of age. Menactra is given to children 24 months or older who have not received a complete series. Two doses of Menactra are administered at least 8 weeks apart and at least 4 weeks after completion of all PCV13 doses for children 24 months and older. Meningococcal B vaccines (Bexsero and Trumenba) are now available vaccine and should be given at 10 years to children who have not received a complete series. Children can receive a two-dose series of Bexsero, at least 1 month apart, or a three-dose series of Trumenba, with the second dose at least 2 months after the first and the third dose at least 6 months after the first. It is important to note that the two meningococcal B vaccines are not interchangeable. The same vaccine product must be used for all doses, or available guidelines should be utilized when combining two different vaccine products. The influenza vaccine should also be provided annually as viral influenza may cause severe morbidity in individuals with SCD [94]. The inhaled flu is not recommended. It is important to note that vaccine responses in SCD may be impaired with documented suboptimal responses to the influenza [95], pneumococcal [96, 97], and other vaccines [98, 99].

Fluids

Patients with SCD often receive additional fluids, regardless of hydration status, as fluids are perceived as beneficial although there is a paucity of data to support this established practice [100]. It is unclear which route (enteral vs. intravenous), amount, and type of fluid administration are optimal [100]. Water content of RBCs is a determinant of intracellular hemoglobin concentration. Even a modest increase in HbS concentration caused by RBC dehydration can precipitate HbS polymerization leading to loss of cell deformability because of the strong concentration dependence of the sickling process [101, 102]. Therefore it has been extrapolated that fluid administration may be beneficial in SCD. A common and early manifestation in SCD is hyposthenuria, an inability to concentrate urine due to progressive infarction of the vasa recta in the renal medulla; therefore patients are prone to dehydration especially in the setting of acute illness [103–105]. Historically, hyperhydration with IV fluids at 1.5 times maintenance has been routinely practiced for patients with VOC [106]. However patients receiving parenteral fluids should be monitored closely for iatrogenic congestive heart failure and electrolyte imbalance [107]. In acute chest syndrome, patients are given fluids at maintenance rate [108] as zealous hypotonic parenteral fluids predispose to pulmonary edema [109]. Furthermore overhydration (like dehydration) of RBCs leads to decreased cell deformability, and there appears to be a water content RBC range where RBCs exhibit optimal rheologic behaviors [110]. In a consensus statement, the NHLBI currently endorses that in euvolemic adults and children with SCD and VOC who are unable to drink fluids, intravenous hydration should be provided at maintenance rate to avoid overhydration. Evidence on the type of parenteral fluid to use in SCD is similarly lacking. As hyposthenuria may cause impaired renal excretion of the sodium load in normal saline, hypotonic solutions have been recommended [111]. However, the induction of hyponatremia hasn't been proven to be of benefit in the management of painful crises [112]. In a recent microfluidic model study of the human capillary system, normal saline was associated with stiffening of RBCs and prolonged transit times [113]. In summary, carefully conducted RCTs are required to elucidate optimal fluid management in patients with SCD.

Evolving Therapies

In recent year many mechanisms and pathways of sickle cell pathobiology have been explored. Understanding of the pathophysiology of SCD has evolved from a simplistic view of chronic hemolysis, vaso-occlusion, and ischemia. SCD is now recognized as an elaborately complex disease state involving several interacting vasculopathic processes consisting of ischemia-reperfusion injury, inflammation,

hemolysis, a procoagulant state, oxidative stress, deficiency of nitric oxide (NO), activation of endothelium, and altered vascular reactivity [114]. A burgeoning area of drug development is targeting these pathways directly to prevent or treat the complications associated with SCD. Some of these drugs under investigation are novel, while others have been used previously for similar or different indications in other diseases. A full account of these therapies is beyond the scope of this chapter and can be found in referenced review articles [115–117]. Some of the promising drugs categorized by their mechanism of actions are listed below. Refer to Chap. 2 for further discussion of many of these pathways being targeted toward drug development.

Drugs Targeting Adhesion

Sickle red cells and leukocytes adhere to endothelium in the microcirculation and contribute to vaso-occlusion [118, 119]. Endothelial selectins (P- and E-selectins) play a critical role in these adhesive interactions. In SCD, inflammatory cytokines upregulate the expression of endothelial E-selectin which along with P-selectin increases adhesion of leukocytes and capture of sickle red cells by leukocytes. The drugs targeting this pathway are attractive therapeutic options for vaso-occlusion. Several selectin inhibitors are currently under investigation. Some of the drugs in this category include IVIG, heparin (tinzaparin), propranolol, and others. Two drugs in this category (GMI-1070 and SelG1) are discussed below [117].

GMI-1070

Also known as rivipansel is a pan-selectin inhibitor initially shown to be effective in sickle mice in improving vaso-occlusion and survival [120]. A randomized, double-blind, placebo-controlled, phase II study of GMI-1070 recruited 12–60-year-old patients with SCD requiring hospitalization for the treatment of VOC. The primary end point of the study was time to resolution of VOC defined as one of the following: decrease in pain score 1.5 cm on visual analog scale from baseline, transition to oral analgesia, or discharge or readiness for hospital discharge. While the primary end point of resolution of vaso-occlusive pain crises was not statistically different between the treatment groups, it showed clinically meaningful reductions in mean and median times to VOC resolution in the GMI-1070 treatment group compared to the placebo group. GMI-1070 was safe without any differences in adverse events between the groups. Additionally mean cumulative IV opioid analgesic use reduced by 83% in patients treated with GMI-1070 [121]. Currently a phase III, multicenter, randomized, double-blind, placebo-controlled study of GMI-1070 is recruiting (clincialtrials.gov NCT02187003).

Crizanlizumab (SelG1)

Crizanlizumab is a humanized monoclonal antibody which binds to P-selectin and results in blockage of its interaction with P-selectin glycoprotein ligand 1 (PSGL-1). A recently completed clinical trial assessed safety and efficacy of crizanlizumab (SelG1) in a phase II, multicenter, randomized, placebo-controlled, double-blind, 12-month study in patients with SCD with or without HU and sickle cell-related pain [122]. Study participants were 16–65 years old with SCD who had 2–10 sickle cell-related pain crises in 12 months before the recruitment in the trial. Patients were assigned to low-dose crizanlizumab (2.5 mg/kg), high-dose crizanlizumab (5 mg/kg), or placebo. The primary goal of the study was to determine the effect of high-dose crizanlizumab on the rate of sickle cell-related crises during 52 weeks of treatment. Patients received two intravenous doses of crizanlizumab or placebo (loading doses) 2 weeks apart and then a maintenance dose every 4 weeks. At the end of the treatment phase, crizanlizumab therapy resulted in a significantly lower rate of sickle cell-related pain crises per year than placebo (1.63 with crizanlizumab vs. 2.98 with placebo). Crizanlizumab was well tolerated and was associated with a 10% rate of adverse events which included arthralgia, diarrhea, pruritus, vomiting, and chest pain [122]. None of the patients developed detectable antibody response during the trial; however long-term follow-up will be needed to detect emergence of late neutralizing antibodies which could limit long-term use of crizanlizumab.

Drugs Targeting Hemoglobin Polymerization

The hallmark of SCD is the polymerization of sickle hemoglobin which results in formation of rigid and sickled erythrocyte which leads to impaired transit of cells and vaso-occlusion. Sickle hemoglobin (HbS) has significantly reduced oxygen affinity as compared to normal hemoglobin (HbA) [123, 124]. Pharmacologic agents that can stabilize the higher oxygen affinity relaxed state (R-state) and/or destabilize the lower oxygen affinity T-state of hemoglobin have the potential to delay the sickling of circulating red cells and may be of clinical benefit. Several compounds with this capability have been described, one of which (GBT400) is being reviewed [125].

GBT440

GBT440 binds to the N-terminal of α-chain of hemoglobin and increases oxygen affinity which leads to reduced polymerization and sickling. In the murine model, this molecule given once daily orally was effective in increasing half-life of erythrocytes, reducing reticulocyte count and sickling (ex vivo) [126]. Currently patients are being recruited on a placebo-controlled study of GBT440 (clincialtrials.gov NCT03036813).

Other Mechanism-Based Therapies Under Investigation

Induction of hemoglobin F has been a long-standing disease-modifying strategy for SCD. Beneficial effects of hemoglobin F on the pathophysiology of SCD are well known, and this approach has been confirmed by the effects of HU therapy in SCD. Besides HU other drugs which augment hemoglobin F production have been in various stages of development and include agents such as decitabine, sodium dimethylbutyrate, vorinostat, and pomalidomide [127–130].

SCD is known to be an inflammatory state. Patients with SCD have chronically elevated white cell counts as well as pro-inflammatory cytokines including TNF, IL-1, and IL-8. In addition to damaged erythrocytes, other cells also contribute to a pro-inflammatory environment. Intravascular hemolysis and release of cell-free hemoglobin and hemin contribute to inflammation and so does increased production of placental growth factor which increases reactive oxygen species. Furthermore role-activated invariant natural killer T (iNKT) cell in SCD pathophysiology has been recently demonstrated and has led to development of a new group of targeted therapies. Drugs being tested in this general category include adenosine 2A receptor antagonist regadenoson; ADP receptor antagonist; ticlopidine, Anagregal; prasugrel; omega-3 acid ethyl esters; a-lipoic acid; *N*-acetyl cysteine; NKTT120; and others [131]. Prasugrel, a thienopyridine P2Y12 ADP receptor antagonist, inhibits ADP-mediated platelet activation and aggregation. Recently a phase II randomized, double-blind, placebo-controlled trial tested its efficacy in children 2 through 17 years of age with SCA who were randomly assigned to receive oral prasugrel or placebo for 9–24 months. The primary end point was rate of vaso-occlusive events which was found to be not significantly lower in the prasugrel compared to placebo [132]. Other agents in this category being tested include omega-3 fatty acid. Omega-3 fatty acid may play a role in reducing inflammation and is being tested for reducing the frequency of vaso-occlusive pain episodes [133]. IVIG has been proposed to inhibit adhesion and activation of leukocytes, and its effect on vaso-occlusive episodes is currently being evaluated in a phase I–II study [134].

Poloxamer-188, a nonionic surfactant with beneficial rheological and antithrombotic properties, was evaluated in a placebo-controlled trial to determine its impact on reducing the duration of the painful episodes. The study showed a significant but small difference between the groups with a 9-hour reduction of pain crisis in the treatment group ($P = 0.04$) [135]. The beneficial effect was more significant in children and in patients receiving HU leading to a recently completed phase III trial in children with SCD. L-arginine is a semi-essential amino acid and NO donor. NO has been implicated in SCD pathology which has been considered a NO-deficient state. Studies in transgenic mice demonstrated that inhibition of arginase improved NO bioavailability and attenuated systemic and pulmonary vascular endothelial dysfunction [136]. Currently, human studies evaluating effect of arginine on pain and other complication of SCD are in various stages of development (clinicaltrials.gov NCT02447874, NCT00513617, NCT01142219, NCT02536170, NCT00004412, NCT01796678, NCT00029731, NCT00056433).

In conclusion, recent advances in the management of SCD have led to its evolution from a life-threatening illness to a chronic disease. Interventions such as universal newborn screening, penicillin prophylaxis, vaccinations along with disease-modifying therapies such as HU and transfusions, and curative HSCT have improved outcomes dramatically for patients living with SCD in developed countries. FDA-approved disease-modifying drug HU has a favorable risk-to-benefit profile in reducing the acute and chronic manifestations of SCD and has a potential to be utilized to improve outcomes in low- and mid-income countries. Improved understanding of the pathophysiology of SCD in recent years has identified new pathways which are being targeted to prevent and treat complications of SCD. Novel therapeutic drugs targeting specific pathophysiologic processes are set to offer an era of mechanistic therapies in SCD.

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