




## Review Article

# Sickle Cell Disease in Children and Adolescents: A Review of the Historical, Clinical, and Public Health Perspective of Sub-Saharan Africa and Beyond

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Sickle cell disease (SCD) is an umbrella term for a group of life-long debilitating autosomal recessive disorders that are caused by a single-point mutation (Glu→Val) that results in polymerization of hemoglobin (Hb) and reversible sickle-shape deformation of erythrocytes. This leads to increased hemolysis of erythrocytes and microvascular occlusion, ischemia-reperfusion injury, and tissue infarction, ultimately causing multisystem end-organ complications. Sickle cell anemia (HbSS) is the most common and most severe genotype of SCD, followed by HbSC, HbS $\beta^0$ thalassemia, HbS $\beta^+$ thalassemia, and rare and benign genotypes. Clinical manifestations of SCD occur early in life, are variable, and are modified by several genetic and environmental factors. Nearly 500 children with SCD continue to die prematurely every day, due to delayed diagnosis and/or lack of access to comprehensive care in sub-Saharan Africa (SSA), a trend that needs to be urgently reversed. Despite proven efficacy in developed countries, newborn screening programs are not universal in SSA. This calls for a consolidated effort to make this possible, through the use of rapid, accurate, and cheap point-of-care test kits which require minimal training. For almost two decades, hydroxyurea (hydroxycarbamide), a century-old drug, was the only disease-modifying therapy approved by the U.S. Food and Drug Administration. Recently, the list expanded to L-glutamine, crizanlizumab, and voxelotor, with several promising novel therapies in the pipeline. Despite its several limitations, hematopoietic stem cell transplant (HSCT) remains the only curative intervention for SCD. Meanwhile, recent advances in gene therapy trials offer a glimpse of hope for the near future, although its use maybe limited to developed countries for several decades.

## 1. Background

Sickle cell disease (SCD) was first described in the western literature by James B. Herrick in 1910 [1]. He reported

peculiar-looking red blood cells (RBCs) for which he had no definite diagnosis at the time. Herrick was alerted about this odd finding by his 27-year-old intern, Ernest E. Irons, who while based in Presbyterian Hospital, had observed

pear-shaped and elongated cells in the blood smear of a 20-year-old negro named Walter Clement Noel. Noel, who was considered by Herrick as “bright and intelligent” was pursuing dentistry at Chicago College of Dental Surgery. Curious to establish the diagnosis, Herrick and Irons continued their follow-up of Noel for 2.5 years after this discovery, a period during which he suffered several severe illnesses. At 32 years, Noel died from pneumonia, 9 years after returning home to Grenada in West Indies [1, 2]. It was after this study that scientists began to decipher the molecular basis and pathophysiologic mechanisms of SCD. Long before Herrick’s report, Horton had identified a clinical phenotype of SCD in the tropics [3]. SCD was described under different names in West Africa, including “Abiku,” “Ogbanje,” and “Sankara-jimi” and was treated using various traditional herbs [4, 5]. Similarly, SCD was well recognized by communities in East Africa as early as the beginning of the 18th century, where it was referred to as “Kagenge” and later “Nnalubiri” by Baganda in present day Uganda. Traditional healers observed characteristic presentations such as recurrent episodes of fever and pain, poor weight and height gain, chronic wounds, and early death; and unsuccessfully attempted to cure the disease using extracts from selected tree leaves and bark [6].

SCD was only recognized as a public health priority by the World Health Organization (WHO) in 2006 [7] and United Nations (UN) in 2008 [8]. In an effort to increase public knowledge and awareness about SCD, the UN recognized June 19 as the World Sickle Cell Day, which was first commemorated in 2009 [9]. SCD is predominant among people of sub-Saharan Africa (SSA), Mediterranean, Middle East, and Indian descent [10]; and has been disseminated across the globe through population migration [11]. Reliable estimates of the global population of individuals with SCD are not currently available, but some authors estimate it to be between 20 and 25 million [12]. More than 312,000 neonates are born with sickle cell anemia (SCA) annually, and 64 to 75% of these are in SSA where 50 to 90% of disease-related deaths occur in childhood [13, 14]. SCD is the most prevalent genetic disorder in the sub-Saharan region of Africa, with approximately 1% to 3% of newborns affected, the highest number of births being in the Democratic Republic of Congo, Nigeria, Tanzania, and Uganda [13–18]. Although projections show that the population of newborns with SCD is rising [14], a large fraction of SCD-related deaths in Africa occur prior to diagnosis, due to the absence of large-scale newborn screening programs [15, 19]. It is unfortunate that in SSA, nearly 500 children aged less than five years die every day due to SCD-related complications [20], with SCD-associated mortality accounting for almost 9-16% of under-five mortality in high-burden countries [21]. Conversely, more than 93% of patients with SCD in developed countries live into adulthood [22], with a median survival age between 58 and 66 years [23].

Despite the fact that many countries in SSA have shown interest in SCD, national policies and funding are still inadequate, mingled with inadequately trained healthcare providers, scarce diagnostic tools, and insufficient treatment [7]. The resultant poor health status and multiple hospitali-

zations of children with SCD tremendously impact on their quality of life and academic achievements, parents’ employability, and productivity, and worsen the already poor socio-economic and psychosocial burden on families in high-burden countries [20].

In this integrated review, we aimed to (1) summarize the pathogenesis and genotypes of SCD, (2) clinical manifestations and complications of SCD in the pediatric population, (3) summarize the comprehensive care package for SCD, (4) underscore the current state of NBS in sub-Saharan Africa and performance of point-of-care tests, (5) highlight evidence of the beneficial effects of currently approved disease-modifying therapy and pipeline drugs, (6) adolescent to adult transition, and (7) prevention of SCD.

## 2. Myths and Misconceptions about SCD in SSA

Several myths and misconceptions are known to influence people’s understanding and care of SCD in Africa and beyond. According to the cultural beliefs of the Igbo in Nigeria, children who are currently defined as those with SCD were conceptualized as those who mysteriously experienced repetitive cycles of birth, death, and reincarnation. They often gave family names that are related to death and performed various rituals after the death of an infant or young child in an effort to stop the reoccurrence of reincarnation [5]. Literature shows that some African communities still believe that SCD is caused by evil spirits/witchcraft or misconduct [4, 24]. In a recent Tanzanian study, participants believed that SCD is for the poor and is a punishment from God [25]. Some men believe that males do not carry the sickle cell gene. Zounon [26] pointed out that lay people in Benin are not sufficiently aware that SCD is inherited; can be detected via genetic testing; does not automatically result in illness; cannot be cured by traditional healers; and that SCD may induce severe kidney, lung, heart, or cerebrovascular complications. Others believe that SCD only affects people of black race; it is blood-borne and contagious; cannot be cured; affected babies do not make it to adulthood; and affected individuals are addicted to pain medication. In addition, some people think that the sickle cell trait can convert into SCD and people with SCD do not suffer from malaria [27, 28]. With this in mind, we strongly recommend that clinicians and concerned stakeholders such as sickle cell foundations and Ministries of Health scale up efforts to continuously sensitize the public about the facts regarding SCD, because these numerous misconceptions adversely influence health-seeking behavior.

## 3. Structure and Function of Normal Hemoglobin

The hemoglobin molecule is a metalloprotein composed of four subunits, each containing a peptide chain and a heme group. The polypeptide chains of hemoglobin are symmetrically paired to form a tetrameric structure and functional unit. Each of the four polypeptides has a large central space into which a heme prosthetic group and an iron protoporphyrin IX molecule are bound by noncovalent forces, thus

protecting the iron atom (Fe<sup>2+</sup>) from access to the surrounding aqueous solution. The alpha ( $\alpha$ ) polypeptide chains and heme group iron protoporphyrin IX are the same in all human hemoglobins. The arrangement of the subunits of hemoglobin (quaternary structure) differs in the oxygenated and deoxygenated states. Oxygen reversibly binds to the ferrous iron atom in each heme group. When oxygen molecules attach to the ferrous iron atoms, the gap between two of the polypeptide chains in the hemoglobin molecule becomes narrower, expanding when oxygen leaves. Besides the transport of oxygen from the lungs to tissues, hemoglobin also interacts with carbon dioxide, carbon monoxide, and nitric acid [29, 30].

Three  $\alpha$  gene clusters (zeta -  $\zeta$ , alpha 1 -  $\alpha_1$ , and alpha 2 -  $\alpha_2$ ) and five  $\beta$  gene clusters (epsilon -  $\epsilon$ , gamma 1 -  $\gamma_1$ , gamma 2 -  $\gamma_2$ , delta -  $\delta$ , and beta -  $\beta$ ) are found at the p13.3 locus of chromosome 16 (16p13.3) and p15.5 locus of chromosome 11 (11p15.5), respectively. During fetal life, Gower 1 ( $\zeta_2\epsilon_2$ ), Gower 2 ( $\alpha_2\epsilon_2$ ), and Portland ( $\zeta_2\gamma_2$ ) hemoglobins are formed because their genes are expressed primarily in the yolk sac, para-aortic region, and the liver. Their downregulation in early embryonic life is followed by the expression of two  $\alpha$  and two  $\gamma$  genes, leading to the formation of fetal hemoglobin ( $\alpha_2\gamma_2$ ), which is the predominant hemoglobin by the 9th week of gestation. Fetal hemoglobin (HbF) has a slightly higher affinity for oxygen than adult hemoglobin because it binds 2,3-biphosphoglycerate (2,3-BPG) less strongly. After birth, the  $\alpha$  genes remain fully active, whereas  $\gamma$  genes are downregulated, and the  $\beta$  cluster genes ( $\beta$  and  $\delta$ ) are upregulated. The adult hemoglobin phenotype is predominant by the end of the first 12 months of life. Normal adult human RBCs contain HbA ( $\alpha_2\beta_2$ ), HbA2 ( $\alpha_2\delta_2$ ), and HbF ( $\alpha_2\gamma_2$ ), accounting for nearly 97%, 2%, and 1% of the total hemoglobin respectively. In rare cases, however,  $\gamma$ -globin gene expression persists in adult RBCs, a condition referred to as hereditary persistence of fetal hemoglobin (HPFH) [29, 30].

#### 4. Genotypes and Pathophysiology of SCD

Sickle cell disease is an umbrella terminology that describes a group of life-long debilitating autosomal recessive disorders which occur as a result of a single-point mutation (base change from GAG to GTG at codon 6, rs334) where a hydrophobic valine replaces hydrophilic glutamic acid at position 6 on the  $\beta$ -globin subunit of hemoglobin (c.20A>T, pGlu6Val) [31–33]. This mutation leads to the formation of an abnormal form of hemoglobin designated as sickle hemoglobin (HbS). Classically, SCD follows an autosomal recessive Mendelian pattern of inheritance where an affected offspring (male or female) receives one defective gene from each parent, as illustrated in Figure 1.

There are variable genotypes of SCD, but the most common is sickle cell anemia (HbSS), which results from inheritance of two copies of the HbS mutation (homozygotes), and accounts for 65% to 70% of all cases of SCD. Other common forms of SCD include hemoglobin SC (HbSC), sickle hemoglobin-beta-zero thalassemia (HbS $\beta^0$ thalassemia), and sickle hemoglobin-beta-plus thalassemia (HbS $\beta^+$ thalas-

emia) which occur when there is coinheritance of mutations responsible for other abnormal types of hemoglobin (i.e., HbC or  $\beta$ -thalassemia) combine with HbS forming a compound heterozygous mutation [32, 34, 35]. Patients with HbS $\beta^+$ thalassemia have reduced levels of  $\beta$ -globin production, while those with HbS $\beta^0$ thalassemia have no  $\beta$ -globin production [32]. HbC is caused by glutamic acid replacement by lysine at the same site as that for HbS (c.19G>A, p.Glu6Lys) [33, 36]. Other  $\beta$ -globin gene mutations include HbD Punjab/Los Angeles (c.364G>C, p.Glu121Gln), HbE, Hb-Lepore, HbO-Arab (c.364G>A, p.Glu121Lys), and Hb Quebec-CHORI, among others [33, 35, 37, 38]. Coinheritance of HbS and these hemoglobin variants leads to rare and relatively benign SCD genotypes (HbSD-Punjab/Los Angeles, HbSE, HbS-Lepore, and HbSO-Arab, HbS-Quebec-CHORI) [39].

Deoxygenation results in intracellular polymerization of molecules of HbS into rigid crystal-like rods which deform the normally flexible biconcave RBCs into the characteristic rigid sickled (crescent) shape [36]. Although polymerization is reversible with reoxygenation, repetitive episodes cause RBC membrane damage and hemolysis [31], reducing the lifespan of RBCs from the normal 90-120 days to 10-20 days [40]. More rapid polymerization occurs with higher concentrations of HbS and low pH but is limited by the presence of HbF. The hallmark pathophysiologic mechanism is the entrapment of sickled RBCs in the microvasculature and the impediment of blood flow, leading to typical acute and chronic ischemic multiorgan complications [31, 34]. Mechanisms are complex and not yet completely understood, but abnormal RBC adhesion, activation of the vascular endothelium, leukocytosis, leukocyte (neutrophils and monocytes) and platelet activation, cellular dehydration, and oxidative stress from tissue reperfusion have been implicated [36, 41, 42]. Molecules such as P-selectin, E-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cellular adhesion molecule-1 (VCAM-1), laminin, and thrombospondin are critical contributors in adhesion [42–44]. This is schematically represented in Figure 2. Increasing knowledge of the pathophysiologic mechanisms that culminate in sickling and subsequent processes has been key in the design of new therapies. Research focus has been set on haptoglobin and hemopexin for their role in binding free extracellular Hb and heme, respectively, HbF-inducing agents (e.g., hydroxyurea, voxelotor), selectin inhibitors (e.g., crizanlizumab), anti-inflammatory agents, antiplatelet agents, anticoagulants, and antioxidants (e.g., L-glutamine) [42, 45–47].

#### 5. Sickle Cell Trait

Sickle cell trait (SCT), not categorized as a SCD, refers to a state where individuals are heterozygous for the sickle allele (HbAS, also known as carriers). It results from inheritance of one abnormal (HbS) allele from one parent and one normal (HbA) allele from another parent [48]. One in every five people has SCT in high-burden countries like Nigeria [49].

Earlier studies characterizing the DNA structure of the  $\beta$ -globin locus of HbS suggest that the mutation arose on at least three independent occasions in the African

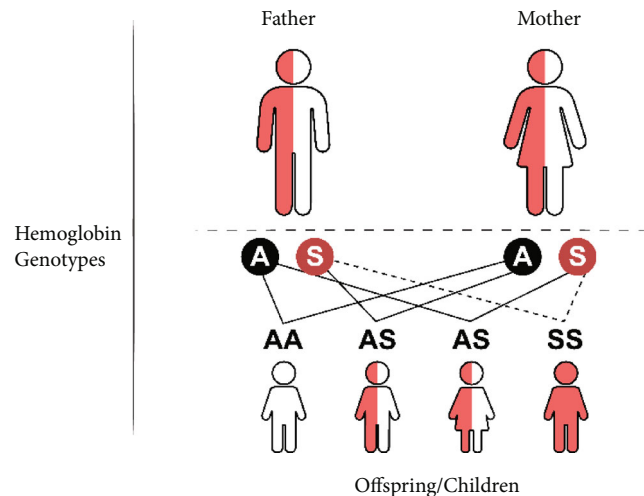


FIGURE 1: Inheritance of sickle cell disease. In a scenario where both parents have a sickle cell trait (SCT, HbAS), each pregnancy carries a 25% chance of normal offspring (HbAA), a 50% chance of offspring with SCT, and a 25% chance of offspring with sickle cell disease (HbSS).

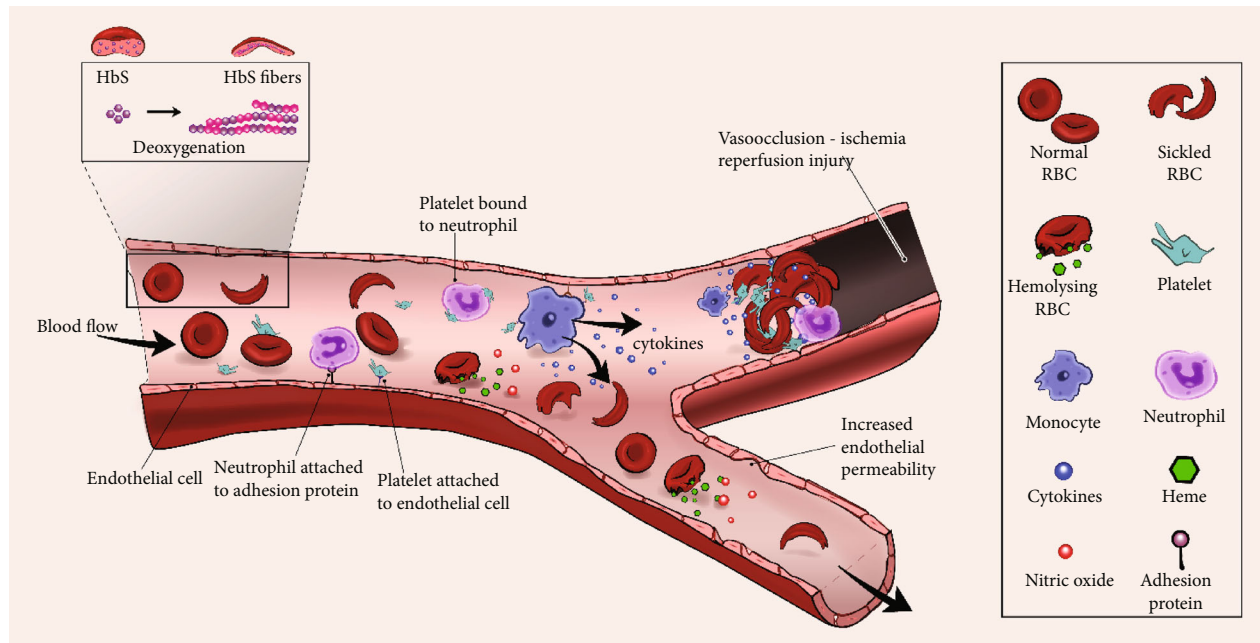


FIGURE 2: Pathophysiologic mechanisms of sickle cell disease. Deoxygenation leads to polymerization of HbS and deformation of RBCs to a sickle shape, making them less flexible. Broadly, RBC, leucocyte, and platelet adhesion are enhanced, and cell-to-cell and cell-to-endothelial interactions occur; there is an upregulation of adhesion proteins (ICAM-1, VCAM-1, P-selectin, and E-selectin); and damage and activation of the endothelium occur. RBC hemolysis releases heme and arginase which scavenge nitric oxide, and stimulates the release of adhesion proteins. Activated platelets cause neutrophils to form neutrophil extracellular traps (NETs), which induce platelet and RBC aggregation; interact with sickled RBCs, neutrophils, and monocytes. Neutrophils also adhere to the endothelium through interaction with adhesion proteins. Monocytes release cytokines, platelet-activating factor, and express tissue factor which upregulate endothelial adhesion proteins, activate platelets, and kickstart the coagulation cascade. Accumulation of leukocytes, platelets, and RBCs with coagulation pathway activation through various mediators leads to the formation of thrombi which are responsible for vaso-occlusion. These events subsequently cause local ischemia and reperfusion injury which leads to organ dysfunction.

continent, referred to as  $\beta$ -globin haplotypes. These haplotypes are determined by restriction fragment length polymorphism (RFLP) and were named after the ethnic group or geographic area where they were first described, namely, Benin (BEN), Senegal (SEN), Cameroon (CAM), Central

African Republic (CAR) or Bantu, and Arab-Indian (AI) haplotypes [50]. Atypical haplotypes have been described in an ethnically diverse Sudanese population with SCA [51]. Results of whole-genome sequencing reveal that the sickle allele had a single origin 259 generations back (7,300



years ago) in West Africa during the Holocene Wet Phase [50]. The distribution of the sickle allele correlates with the distribution of malaria [52]. Worldwide, nearly 5.5 million neonates are born with SCT annually, 65% of them in the WHO African region, where malaria is highly prevalent [14]. SCT confers a significant survival advantage in regions of high malaria endemicity. A 2014 multicenter study of 11,890 cases of severe *Plasmodium falciparum* malaria and 17,441 controls recruited from 12 locations in Africa (The Gambia, Mali, Burkina Faso, Ghana Navrongo and Kumasi, Nigeria, Cameroon, Kenya, Tanzania, and Malawi), Asia (Vietnam), and Oceania (Papua New Guinea) found that people with HbAS have an 86% lower risk of developing severe malaria [53]. Individuals with SCT are usually clinically asymptomatic [34] and have a normal life expectancy similar to unaffected people, but are not necessarily free of adverse outcomes. Accumulated evidence shows that they have a high risk of vaso-occlusive pain, hyposthenuria, proteinuria, hematuria, renal medullary carcinoma, venous and pulmonary thromboembolism, and rhabdomyolysis following extreme physical exertion [36, 54–56]. Nonetheless, these events are rare.

## 6. Newborn Screening for SCD in Sub-Saharan Africa

**6.1. Current State of NBS Programs in SSA.** Early diagnosis and initiation of comprehensive care for genetic diseases like SCD can be life-saving. This can be achieved prenatally through chorionic villus sampling or amniocentesis, or postnatally through newborn screening [32]. Although universal NBS programs have been successful in developed regions such as Europe [35, 57] and North America [58], this has not been prioritized by countries in sub-Saharan Africa where many of the targeted NBS initiatives are still in infancy, mostly limited to feasibility and pilot studies, and in a few centers [18, 59–61]. Universal NBS has not been widely implemented even in Ghana [17] and Benin [59] where substantial progress in NBS research capacity and follow-up has been documented since the early 90s. In Uganda, screening for SCD is focused on children aged 24 months or less, and in districts with the highest burden of SCD [18]. Certainly, we need to acknowledge the numerous limitations to the expansion of the program in SSA [62].

McGann [15] in his advocacy for countries to prioritize SCD suggests that NBS programs in Africa can sustainably be integrated into already existing infrastructure such as the expanded program of immunization and the HIV early infant diagnosis (HIV-EID) at a low cost. A notable example is the study by Ndeezi et al. [63] which determined the prevalence of sickle cell trait and SCD using dried blood spots that are routinely collected from HIV-exposed infants across Uganda. In Nigeria, Nnodu and colleagues [16] demonstrated that NBS can be feasibly implemented through integration into the routine immunization structure with minimal additional human resource and finances. In Ghana, newborns are screened for SCD at birth, at well-infant clinics, or within a few weeks after birth [17]. Newborns delivered outside health facilities can be screened during

their first vaccination. However, there is a need to raise public awareness about the relevance of newborn screening and early interventions through concerted efforts by Ministries of Health and partners [49, 64].

An innovative collaboration between the American Society of Hematology (ASH), hematologists and public health specialists in SSA, and the Consortium on Newborn Screening in Africa (CONSA) was launched in 2020 to demonstrate the benefits of NBS and early access to clinical interventions at participating institutions in 7 countries, including Kenya, Ghana, Liberia, Nigeria, Uganda, Tanzania, and Zambia [64]. The pilot project aims to screen 10,000 to 16,000 babies per year in each country for five years, while providing clinical follow-up for newborns with SCD [64]. However, the sustainable implementation of such major projects in low- and middle-income countries following the withdrawal of major funding institutions remains a key challenge, often driven by health priorities and funding.

**6.2. The Value of Point-of-Care Testing for NBS.** Conventional methods for performing NBS such as hemoglobin electrophoresis, isoelectric focusing (IEF), DNA testing, and high-performance liquid chromatography (HPLC) require expertise, expensive equipment, reagents, electricity, and long-distance transportation of blood specimens and laboratory results [18, 65]. Wide-scale implementation is also challenging in low-resource countries because of the high turnaround time for results, and yet, locating the family afterward is often difficult [65]. In many health facilities in Africa, the sickling test and sickle solubility test are readily used to screen for SCD. However, these tests do not differentiate SCT from SCD [66]. Using standard methods such as hemoglobin electrophoresis makes it possible to differentiate hemoglobinopathies in the newborn, based on the Hb types present. Normal screening results show HbF and HbA (F, A). Sickle cell trait (F, A, S); HbSS, HbS- $\beta^0$ thalassemia, or HbS-HPFH (F, S); HbSC (F, S, C); HbS $\beta$ -thalassemia (F, S, A); SCT with  $\alpha$ -thalassemia trait (F, A, S, Barts); and  $\beta$ -thalassemia major (F) can be diagnosed [32].

A rapid, easy to use, accurate, and cheap point-of-care test (POCT) for SCA is key in making widespread screening possible and efficient [15]. A pilot study of newborns and infants younger than 9 months who presented for immunization at five primary health facilities in Nigeria showed that POCTs are accurate and reliable [16]. By using two lateral flow immunoassay POCTs (HemoTypeSC<sup>TM</sup> and Sickle SCAN<sup>TM</sup>), both tests had a specificity of 100% and a sensitivity of 100% for detection of SCD when compared to high-performance liquid chromatography as a gold standard. An earlier multicenter study involving 1,121 neonates and infants at 18 health facilities in Nigeria found a 93.4% sensitivity and 99.9% specificity of HemoTypeSC<sup>TM</sup> rapid test kit for the diagnosis of SCA, with an overall accuracy of 99.1% in field conditions [67]. In a study conducted across three study sites in Ghana, Martinique, and USA, HemoTypeSC<sup>TM</sup> had an overall sensitivity and specificity of 99.5% and 99.9%, respectively across all hemoglobin phenotypes, 100% sensitivity and specificity for SCA, and >99% sensitivity and specificity for detection of normal and trait states [68]. Similar

results were documented by researchers using HemoTypeSC™ in Nigeria [69] and Côte D'Ivoire [70], and using Sickle SCAN™ in Mali and Togo [71].

POCTs require only 1 to 5  $\mu$ L of blood from a finger prick. POCTs identify HbA, HbS, and HbC, and can therefore diagnose the HbAS, HbSS, HbSC, and HbCC phenotypes; but they cannot quantify different hemoglobins or accurately identify other forms of SCD such as HbS $\beta$ -thalassemia [72]. The cost of one POCT ranges from US\$1.49 to US\$5.09, with results available in approximately 10 minutes through visual inspection of the test line color intensity [16, 68, 73]. Moreover, the test requires minimal operator training, with no need for electricity, refrigeration, or other instruments [68]. Unfortunately, these tools have not translated into national NBS programs, as many nationwide NBS programs are pilot projects.

## 7. Helping Families Cope with a Diagnosis of SCD

It is not uncommon for health practitioners to slap a new diagnosis without due consideration of the emotional distress and the feeling of guilt that parents experience. Many parents in Africa have limited knowledge about SCD and thus view it through socio-cultural, religious, and economic dimensions. Some communities believe that SCD is a curse to their families and worry about social stigma and medical expenses [74, 75]. Individuals with SCD are perceived to be witches and wizards. Some parents pay less attention and invest less because they link the diagnosis to early child mortality and "recurrent" death, which undermines their survival [75]. Parents may initially deny the diagnosis and fail to comply with medical recommendations. Fathers may deny paternity, accuse women of sexual unfaithfulness, and blame them for being responsible for SCD, resulting in family separation [76]. Therefore, a face-to-face interaction is crucial when announcing the results, considering the importance of pretest and post-test counselling [72]. Parents need support to focus on the expected achievements and future personal and professional life of their children. This can be achieved by thorough education of parents about SCD (genetics, transmission, and care), sharing experiences among affected families, provision of psychological support [65], and linkage to a sickle cell treatment center.

## 8. Clinical Presentation of SCD

Clinical manifestations of SCD occur at a time when  $\gamma$ -globin chain synthesis decreases and is replaced by  $\beta$ -globin chain synthesis. This leads to decreased production of HbF and increased production of HbS, at a transition rate that varies among individuals [48]. Typically, HbF levels drop during the first few months of life from nearly 85% of the total hemoglobin at birth to less than 1% at 12 months of life, accompanied by increased synthesis of HbA in normal individuals [77]. Individuals with HbSS and HbS $\beta^0$ thalassemia have the most severe clinical and hematologic phenotype, whereas those with HbSC and HbS $\beta$ +thalassemia have a less severe spectrum of manifestations. The baseline

hemoglobin level for patients with HbSS and HbS $\beta^0$ thalassemia ranges from 6 to 9g/dl, while that of HbSC and HbS $\beta$ +thalassemia ranges from 9 to 11g/dl and 10 to 12g/dl respectively [32]. For unknown reasons, patients with HbSC and HbS $\beta$ +thalassemia are more prone to proliferative sickle retinopathy which can lead to loss of vision [48, 78]. Our discussion will mainly focus on SCA because it is the most prevalent and most severe form of SCD in SSA.

Individuals with SCA experience numerous multisystemic complications (Table 1). Infants with SCA may present with dactylitis (hand-foot syndrome) and splenic sequestration as early as 3 months of life [48]. Dactylitis affects up to 45% of children by 2 years of life [79], becoming rare after 5 years of life. Other common manifestations include jaundice, anemia, acute chest syndrome (ACS), and overwhelming infections. Children experience acute and chronic pain of varying intensity, jaundice, anemia, splenic sequestration, ACS, stroke, infections, poor nutritional status, poor academic performance, and delayed puberty [34, 48], among other complications [80] (Tables 1–4). Adolescents exhibit enuresis, priapism, chronic leg ulceration, increased vaso-occlusive bone pain episodes, avascular necrosis of the hip, and delayed physical growth and puberty, which require significant clinical and psychosocial support [48]. The most common reasons for hospitalization include vaso-occlusive pain, severe anemia, infections, stroke, and acute chest syndrome [81, 82]. Triggers of crises range from dehydration to cold exposure, physical exertion, psychological stress, injury (e.g., following surgery), infections or infestations, pregnancy, smoking, and drugs, among others [24, 40, 49].

## 9. Predictors of SCD Severity

Genetic and environmental modifiers have been found to result in considerable variability of clinical phenotypes, given that some individuals experience milder symptoms and live longer, whereas others live with frequent and severe complications and premature mortality [84, 85]. In as much as SCD has been well studied, the complex effect of genetics on disease phenotype is yet to be deeply understood and may provide an additional window for targeted disease-modifying treatment and prognostication [46, 86].

A study of 9 identical twins and 350 age-gender-matched sibling pairs in Jamaica found no significant differences among identical twins with SCD regarding attained height for age, weight for height, HbF levels, total Hb, mean cell volume, mean cell hemoglobin and total bilirubin levels, occurrence and grade of splenomegaly, susceptibility to priapism, and age at menarche. The occurrence and severity of other complications (e.g., acute chest syndrome, aplastic crisis, cerebrovascular events) were variable, suggesting the contribution of nongenetic (environmental) factors [87].

*9.1. Environmental Factors.* The contribution of factors such as environmental temperature, air quality, bacterial and viral infections, malaria, nutritional status, socioeconomic status, physical activity, and public health measures (e.g., immunization) on the clinical expression and outcome of SCD

TABLE 1: Clinical presentation and complications of SCD.

System/organ	Complications
Neurological	Stroke (hemorrhagic or ischemic)
Eyes	Retinopathy
Respiratory	Acute chest syndrome, asthma
Cardiovascular	Cardiomyopathy, left ventricular hypertrophy, pulmonary artery hypertension (PAH), venous thromboembolism
Spleen	Acute splenic sequestration, chronic splenomegaly
Hepato-biliary	Sickle hepatopathy (hepatic sequestration, viral hepatitis, sickle cell intrahepatic cholestasis, cholelithiasis), transfusion iron overload
Renal	Proteinuria, painless hematuria, hyposthenuria, renal impairment/failure
Genital	Priapism
Bones and joints	Acute vaso-occlusive pain crisis, chronic pain, avascular necrosis, aplastic crisis, multifocal osteomyelitis, septic arthritis, fronto-occipital bossing, gnathopathy
Skin	Chronic leg ulcers
Other	Infections, girdle/mesenteric crisis, delayed growth and puberty, jaundice, pallor, depression, anxiety, and poor academic performance

References: [32, 34, 39, 46, 48, 49, 80, 83].

cannot be underestimated [48, 88]. More prospective studies need to be conducted in this area.

Available evidence shows that cigarette smoking, whether active or passive smoke exposure, results in increased hospitalization for vaso-occlusive pain and acute chest syndrome [89, 90]. Components of cigarette smoke displace oxygen from hemoglobin, damage the vascular endothelium, and lead to platelet aggregation and thrombus formation [90]. This data suggests that decreasing tobacco smoke exposure for children with SCD could lower morbidity, mortality, and medical expenses [90]. Unfortunately, this concept is not addressed in sickle cell treatment guidelines.

**9.2. Genetic Factors. Fetal hemoglobin:** HbF is probably the most extensively studied modulator of SCD severity. Patients with SCA have HbF concentrations ranging from 0.1% to 30%, with an average of 8% [86]. Children with higher HbF levels are less likely to be hospitalized [82]. Hereditary persistence of fetal hemoglobin is a rare benign disorder which presents with high HbF levels of approximately 30% that persists into adulthood. HPFH can be deletional or non-deletional and have a pancellular or heterocellular distribution. Tolu and colleagues [91] observed that individuals who coinherit HPFH and SCD have a delayed onset of severe complications, although this survival advantage attenuates with increasing age. There is no doubt that the polymerization-inhibiting effect of HbF depends on the distribution of HbF in RBCs [77]. Perhaps, a good predictor of disease severity is the distribution of HbF concentrations among F-cells (a subset of erythrocytes that contain HbF), and not total HbF or F-cell percentages [77, 92].

**$\alpha$ -thalassemia:** In the African population,  $\alpha$ -thalassemia mainly occurs as a result of 3.7 kb  $\alpha$ -globin gene deletions ( $^{-3.7}\alpha_2/\alpha_1\alpha_2$  or  $^{-3.7}\alpha_2/^{-3.7}\alpha_2$ ) [93, 94]. Co-existence of  $\alpha$ -thalassemia in individuals with HbSS results in reduced mean corpuscular hemoglobin concentration (MCHC), reduced intracellular HbS concentration and HbS polymerization,

lower number of irreversibly sickled RBCs, higher hematocrit, higher age at diagnosis, and fewer visits to the hospital [82, 94–96]. The median RBC count increases, whereas the median mean corpuscular volume (MCV) and WBC count significantly decrease with increasing number of  $\alpha$ -globin gene deletions [94]. Through a study to determine the frequency of deletional  $\alpha$ -thalassemia among blacks with SCA in the United States and Africa, Mears and colleagues [97] revealed a frequency of 0.12 to 0.16 in normal participants and 0.18 to 0.20 in those with SCT. The frequency was significantly high among patients with SCA, ranging from 0.22 to 0.33. There was a significant association between increasing age and the frequency of deletional  $\alpha$ -thalassemia, implying that individuals with SCA and  $\alpha$ -thalassemia live longer. This finding has been replicated by other researchers in Africa [94].

**HbS haplotypes:** Powars and Hiti [96] demonstrated that patients with CAR haplotype have the most severe progression of clinical manifestations and are more likely to die during the first three decades of life; those with the Senegal haplotype have less severe disease, whereas those with the Benin haplotype had intermediate severity. This is because individuals with Senegal and Benin haplotypes have high HbF levels compared to the CAR haplotype [96, 98, 99]. The Arab-Indian haplotype is associated with the highest HbF levels and frequent  $\alpha$ -thalassemia, which inhibit sickling and ameliorate the clinical severity of the disease [48, 100].

## 10. Comprehensive Care of Children with SCD

**10.1. Overview.** The main goal of care is to improve the quality of life and life expectancy of individuals with SCD [24, 49]. This is achieved through coordinated care in community settings, primary care and specialist practices, emergency departments, laboratories, and sickle cell clinics in hospitals [83]. Comprehensive care of children with SCD includes simple proven measures such as patient/caregiver

TABLE 2: Drugs used in sickle cell disease.

Drug	Recommended dose	Frequency	When to stop	Comments
Phenoxymethyl penicillin (Pen-V)	<1 year: 62.5mg 1-3 years: 125 mg ≥3 years: 250 mg	Oral, twice daily, beginning at 3 months of life	5 years, unless child had splenectomy or invasive pneumococcal infection	Prophylaxis against encapsulated bacteria
Erythromycin	Same dose as Pen-V			
Sulfadoxine-pyrimethamine (e.g., Fansidar)	<2 years: ½ tablet 2 to 5 years: 1 tablet >5 years: dose based on weight	Oral, once every month	Life-time	Prophylaxis against malaria Begin from age >2 months
Proguanil	<1 year: 25mg 1-3 years: 50mg 3-6 years: 50-100mg >6 years: 100-200mg			
Folic acid	<1 year: 62.5 – 2.5 mg 1-3 years: 2.5 mg ≥3 years: 5 mg	Oral, once daily	Life-time	All children aged <3 years may receive 2.5mg daily
Hydroxyurea	15-20 mg/kg/day initial dose (max=35mg/kg/day)	Oral, once daily	See section 10.5	Escalate starting dose by 2.5 to 5mg/kg every 8 weeks until clinical response or hematological adverse effects
L-glutamine <sup>a</sup>	<30 kg: 5g (1 packet) 30-65 kg: 10g (2 packets) >65 kg: 15g (3 packets)	Oral, twice daily		Given to patients aged ≥5 years
Crizanlizumab <sup>a</sup>	5 mg/kg/dose	Intravenous, repeat dose after 2 weeks of the first, then every after 4 weeks		Given to patients aged ≥16 years
Voxelotor	1500 mg	Oral, once daily		Give to patients aged ≥12 years Improves anemia

<sup>a</sup>Can be given with or without hydroxyurea. References: [10, 24, 33, 49, 83, 105, 113, 125].

education on early identification of clinical presentations of life-threatening complications such as fever, severe anemia, and splenomegaly, pneumococcal, *Hemophilus influenzae* type b (Hib) and meningococcal vaccines, prophylactic anti-malarials and penicillin, analgesics, nutritional supplements, blood transfusion, disease-modifying drugs, and planned clinic evaluations [32, 34, 49, 65, 101, 102]. These measures can be categorized as supportive (balanced diet, folic acid, and hydration), preventive (chronic blood transfusion to prevent stroke, hydroxyurea, L-glutamine, crizanlizumab, voxelotor, penicillin prophylaxis, and pneumococcal vaccination), symptomatic (antibiotics, blood transfusion, and analgesics), and curative (hematopoietic stem cell transplant) approaches. Compliance to these measures results in

improved physical growth, a remarkable reduction in the frequency and severity of acute events requiring hospitalization, and lower mortality [102]. A summary of recommended drugs and health monitoring of children with SCD is provided in Tables 2 and 3, respectively. Table 4 summarizes the clinical manifestations, evaluation, and management of acute complications associated with SCD.

Major drawbacks to the implementation of comprehensive care measures in SSA include the existence of specialized care facilities in large cities [65], absence of comprehensive SCD treatment guidelines in many health facilities [103, 104], limited access to approved disease-modifying drugs, and ultimately, scarcity of health practitioners. It is obvious that up-to-date clinical protocols



TABLE 3: Screening/health monitoring of children and adolescents with sickle cell disease.

Investigation	Relevance	Timing	Interpretation of findings and interventions
TCD	Screening for risk of stroke		Normal (all mean velocities <170 cm per sec). Continue TCD annually
	Assesses blood velocity in the distal internal carotid, anterior or middle cerebral artery	Begin at 2 years of age and continue until at least 16 years of age	Conditional (mean velocity 170 to 199 cm per sec) <sup>‡</sup> Initiate hydroxyurea therapy Abnormal (mean velocity ≥200 cm per sec). Repeat TCD within 2 to 6 weeks. Start long-term transfusion therapy. If not possible, initiate HU therapy Inadequate (no information available on one or both middle cerebral arteries)
Ophthalmoscopy (Dilated retinal exam)	Ischemic retinopathy	Begin at 10 years, then every 1-2 years if normal	Refer patients with suspected retinopathy to a retinal specialist for possible laser photocoagulation therapy
Echocardiography	Screening for PAH		
Transcutaneous O <sub>2</sub> saturation		Begin at 12 months, continue annually or more frequently based on clinical course	
Complete blood count with WBC differential and reticulocyte counts		Every 3 months beginning from 3 months of life, then every 6 months after 2 years of life	Frequency adjusted based on the patient's clinical state
Liver and renal function tests	Routine screening	Every 6 months	
HbF percentage		Every 6 months for children aged 6 to 24 months, then annually	
Spot urine testing	Microalbuminuria and proteinuria. Early markers of renal dysfunction	Begin by 10 years of life, and then annually if negative	If proteinuria (>300 mg per 24 hours), perform a first morning void urine albumin-creatinine ratio or 24-hour urine creatinine clearance. Consult/refer to nephrologist if abnormal ACEIs may be indicated

TCD: transcranial Doppler ultrasonography; ACEI: angiotensin-converting enzyme inhibitors. <sup>‡</sup>Repeat TCD USS after 3 months, then every 4 months. References: [10, 24, 49, 83, 122, 126, 127].

facilitate uniformity and standardization of care across different health facilities [49]. Until more recently, several high-SCD-burden countries lacked published SCD diagnosis and treatment guidelines. For instance, national guidelines for Nigeria were released in 2014 [49], whereas those of Uganda [24], Tanzania [105], and Kenya [72] were released in 2020. In as much as the recommendations in these guidelines are evidence-based, a very small fraction of health facilities in SSA have the necessary infrastructure and human resource to perform investigations such as transcranial Doppler ultrasonography (TCD) screening and extended phenotyping of blood to reduce the risk of alloimmunization [65], and neuroimaging. More worrying is the rarity of dedicated SCD care centers or clinics in the region. As such, children with SCD are queued in general clinics where they receive less attention. To facilitate improvement in SCD care in these settings, we suggest the development of handbooks [106] and their widespread distribution and clinician training of basic guidelines.

**10.2. Malaria Chemoprophylaxis.** Malaria chemoprophylaxis combined with mosquito net use, early diagnosis, and treatment are established preventive strategies in regions where malaria is highly prevalent. Sulfadoxine-pyrimethamine (SP), sulfadoxine-pyrimethamine + amodiaquine, pyrimethamine, proguanil, chloroquine, mefloquine, and mefloquine-artesunate are among the drugs that have been studied in sub-Saharan Africa [107]. Studies showed that monthly SP has greater potential to reduce episodes of malaria compared to weekly chloroquine [108] and daily proguanil [109]. Chemoprophylaxis reduces hospitalization rates, blood transfusion requirements, and symptoms such as vaso-occlusive pain [107, 110, 111], with good tolerability [107, 112].

**10.3. Penicillin Prophylaxis and Pneumococcal Vaccination.** Development of functional asplenia in children with SCA makes them susceptible to fulminant infection by encapsulated organisms, particularly *Streptococcus pneumoniae*, but also by *Hemophilus influenzae type b* and *Neisseria*

TABLE 4: Diagnosis and treatment of acute complications of SCD.

Complication	Clinical presentation and evaluation	Treatment
Fever	<p>May be a manifestation of an acute and sometimes life-threatening complication such as acute chest syndrome (ACS) or osteomyelitis.</p> <p>CBC with WBC differential, reticulocyte count, blood culture, and sensitivity. Perform urine culture and lumbar puncture for CSF analysis if urinary tract infection or meningitis is suspected respectively. Chest X-ray if signs of ACS</p>	<p>Immediate medical attention</p> <p>Temperature <math>\geq 39.5^{\circ}\text{C}</math>: admit to hospital for a 7-day course of IV antibiotics and close monitoring.</p> <p>Temperature <math>\geq 38.5^{\circ}\text{C}</math>: administer IV antibiotics with coverage against <i>Streptococcus pneumoniae</i> and gram-negative enteric organisms (e.g., ceftriaxone, 75-100 mg/kg), then subsequent outpatient care and follow-up within 24hr. Continue with an oral antibiotic is feasible in patients who do not appear ill or toxic looking.</p> <p>Subsequent antibiotic change should be based on culture and sensitivity results</p>
Vaso-occlusive crises (VOC)	<p>Manifests as sudden or gradual excruciating pain, most commonly in limbs, back, chest, and abdomen. Triggers include infections, stress, and cold exposure, among others</p> <p>Determine associated symptoms, location, and severity of pain</p> <p>Severity of pain is based on the patient report. Use a pain severity assessment scale such as the Wong-Baker faces</p>	<p>Treatment is individualized. Depends on severity of pain, patient or caregiver knowledge of predictably effective agents and doses, and previous adverse events. Initiate analgesics within 30 minutes of triage.</p> <p><b>Mild pain:</b> non-opioid analgesics. Paracetamol 15mg/kg/dose 4 to 6hrly (maximum = 60mg/kg/day) +/- Ibuprofen 5-10mg/kg/dose 6-8 hrly OR diclofenac 1mg/kg PO/suppository 8hrly +/- adjuvants (i.e. anxiolytics, antidepressants)</p> <p><b>Moderate pain:</b> non-opioid analgesics as above alternated with an opioid, e.g., codeine 0.5-1mg/kg every 3-4 h, dihydrocodeine 1mg/kg/dose 8hrly, oral oxycodone 0.15-0.20 mg/kg every 3-4 h, hydrocodone 0.15-0.20 mg/kg every 3-4 h, and tramadol IV 2 hr, +/- adjuvants</p> <p>Ketorolac 0.5 mg/kg/dose 6 hr (max=30mg/dose, 60mg/day). Avoid use with other NSAIDs.</p> <p><b>Severe pain:</b> Oral morphine sulfate 0.2-0.4mg/kg/dose (max=20mg/dose) or diamorphine 0.1mg/kg/dose in IV infusion or IM/SC stat for immediate pain relief, then maintenance oral morphine 0.2-0.4mg/kg/dose 3-4 hourly. IV diclofenac 1mg/kg/dose 8 hourly after opioids</p> <p>Morphine IV or SC (0.05–0.15mg/kg over 10 minutes) 2-4hr or hydromorphone IV 0.015-0.020 mg/kg 3-4hr. In case of opioid-induced respiratory depression, give naloxone IV 10 <math>\mu\text{g/kg}</math> (Max=8mg). Patient-controlled analgesia (PCA) may be provided Consider ketamine infusion at analgesic dose (0.1–0.3 mg/kg/hr, Max=1 mg/kg/hr) if pain is refractory to opioids</p> <p>When using morphine, administer laxatives (e.g., lactulose, senna) because it can cause constipation. Treat pruritus (itching) after opioid administration using oral antihistamines, and nausea/vomiting using antiemetics</p> <p>Avoid meperidine (risk of neurotoxicity – dysphoria, irritable mood, clonus, and seizures) unless it is the only effective opioid (0.75-1.0 mg/kg 3-4hr)</p> <p>Reassess patient after every 15-30 minutes to determine effectiveness of pain medication (+adverse events) and adjust accordingly</p> <p>Oral hydration. If unable to drink fluids, provide IV hydration at maintenance fluid rate</p> <p>Oxygen therapy if SPO2 &lt;95% on room air</p> <p>Adjunctive nonpharmacological approaches (e.g., local warm application, massage, reassurance, and</p>

TABLE 4: Continued.

Complication	Clinical presentation and evaluation	Treatment
		<p>distraction through stories and play)            Psychosocial support            Rule out and treat malaria or bacterial infections (including osteomyelitis, septic arthritis) if confirmed, avascular necrosis, ACS            Do not transfuse with blood unless other indication is present</p>
Splenic sequestration crisis	<p>Due to sudden progressive enlargement of the spleen caused by pooling of blood in the spleen. Quick drop in Hb level <math>\geq 2</math> g/dL below the baseline value. Can cause hypovolemic shock and death.</p> <p>Common in children &lt;6 years with HbSS and some older children and adults with HbSC or HbS<math>\beta</math>-thal</p> <p>CBC and reticulocyte count (reticulocytosis, elevated circulating nucleated RBCs, anemia, and thrombocytopenia)</p>	<p>10ml/kg of packed RBCs or 15ml/kg of whole blood over 2-4hr to raise Hb to stable level, but not exceeding 8g/dl. Risk of hyperviscosity.</p> <p>Immediate IV fluid resuscitation if hypovolemia – normal saline 20ml/kg</p> <p>Monitor vitals            Analgesics for pain            Investigate and treat infections, malaria            Monitor splenic size 12-24hr            Splenectomy if <math>\geq 2</math> episodes occur, and in patient with chronic hypersplenism</p>
Aplastic crisis	<p>Acute acquired red cell aplasia caused by parvovirus B19 infection</p> <p>Presents with weakness and easy tiredness, fever, facial erythema, headache, severe anemia, and low reticulocytopenia (&lt;2% of total RBC count)</p>	<p>Isolate patient – droplet precautions</p> <p>Transfuse with RBCs. Target to achieve the patient's steady-state Hb level</p>
Acute chest syndrome	<p>Caused by pulmonary infection, sequestration of RBCs in pulmonary vasculature, and fat embolism. May follow VOC or surgery</p> <p>Associated with high mortality</p> <p>Presents with cough, chest pain, difficulty in breathing, <math>\pm</math> fever. Examination may be normal or reveal signs of respiratory distress, hypoxemia, wheezing, percussion dullness. Consider two or more of the above.</p> <p>New opacity on a chest X-ray</p> <p>Perform CBC, blood grouping and cross-matching, CRP, blood gas analysis if in respiratory failure</p>	<p>Hospital admission</p> <p>Oxygen therapy if low O<sub>2</sub> saturation (target SPO<sub>2</sub> &gt;95%)</p> <p>Antibiotics: Third generation cephalosporin (e.g., ceftriaxone 80-100 mg/kg/day for 7-10 days) combined with an oral macrolide for Mycoplasma and Chlamydia coverage: azithromycin 5-10mg/kg (max dose 500mg) once daily for 5 days or erythromycin 5-10 mg/kg/dose (max dose 500mg) 6 hourly for 7-10 days</p> <p>Bronchodilators (e.g., nebulized salbutamol 2.5 mg for children &lt;5 years, 5mg for older children)</p> <p>Analgesics</p> <p>If Hb concentration is &gt;1.0 g/dL below baseline, consider simple blood transfusion with 10mL/kg of packed RBCs or 20ml/kg of whole blood. Urgent exchange transfusion if rapid progression of ACS</p> <p>Optimal hydration (avoid pulmonary edema)</p> <p>Monitor vitals and for acute anemia</p> <p>Incentive spirometry every 2–4 hours while awake</p>
Acute stroke	<p>Ischemic and hemorrhagic stroke are mostly common in children and adults respectively</p> <p>Headache, vomiting, seizures, sensory/motor neurological deficits (paresis, hemiplegia, paraplegia, facial droop, aphasia), altered level of consciousness/coma</p> <p>MRI and MRA, acute brain infarct or hemorrhage</p> <p>CT, acute hemorrhage in the brain</p> <p>Exclude meningitis</p>	<p>Monitor vitals, maintain normal temperature</p> <p>Exchange blood transfusion within 4 hours if acute stroke is confirmed by neuroimaging</p> <p>Initiate long-term blood transfusion every 3-4 weeks and/or Hydroxyurea (if monthly transfusion unavailable)</p> <p>Physiotherapy in the long-term</p>
Priapism	<p>Presents as a sustained and painful erection unrelated to sexual stimulation. Lasts <math>\geq 4</math> hours (fulminant or major) or repeated painful erections lasting more than 30 minutes and up to 4-6 hours (stuttering)</p> <p>Erectile dysfunction and impotence can result from delay in diagnosis and treatment</p>	<p>At onset (&lt;2hr): encourage extra oral fluids</p> <p>Oral or parenteral analgesia</p> <p>Attempt to urinate</p> <p>Warm bath</p> <p>Exercise (e.g., walking)</p> <p>Anxiolytics if anxious (e.g., lorazepam 0.05mg/kg/</p>

TABLE 4: Continued.

Complication	Clinical presentation and evaluation	Treatment
		dose 8-12hr, Max= 2mg/dose) If >2hr, catheterize if unable to urinate, consult urologist or surgeon – to consider irrigation and aspiration of the corpus cavernosum and intracorporeal etilefrine or phenylephrine injection If no response to initial treatment, consider simple or exchange blood transfusion
Multisystem organ failure (MSOF)	Associated with VOC and characterized by respiratory, hepatic, and renal failure Unexpected and rapid deterioration, usually after several days of in-hospital treatment for severe VOC, at a time when pain is beginning to improve Fever, non-focal encephalopathy, ACS. Rapid decline in Hb and platelet count. Marked elevations in liver enzymes, total and direct bilirubin, blood coagulation screening tests. Elevated serum creatinine ( $\pm$ oliguria and hyperkalemia)	Rapid diagnosis and treatment Simple or exchange blood transfusion to Hb 10g/dL Supplemental oxygen and mechanical ventilation (if needed) Renal replacement therapy (e.g., hemodialysis) for acute renal failure (if needed)
Acute severe anemia	Hemoglobin <5g/dl or acute drop of Hb by >2g/dl from baseline/ steady state or acutely symptomatic anemia Rule out malaria, bacterial infections, splenic or hepatic sequestration, and aplastic crisis	Immediately transfuse with packed RBCs 10ml/kg if symptomatic or Hb <5g/dl Transfuse to steady-state Hb if asymptomatic and Hb >5g/dl Treat patient according to other underlying diagnoses

CT: computerized tomography; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging. References: [24, 49, 72, 83, 105, 106, 125, 126, 128, 129].

meningitidis [113]. Other organisms include *Escherichia coli*, *Staphylococcus species*, *Pseudomonas species*, *Salmonella species*, *Enterobacter species*, *Acinetobacter species*, and *Klebsiella species* [113, 114]. Results of a landmark study [115] showed that twice daily penicillin prophylaxis significantly reduces the incidence and mortality associated with *S. pneumoniae* septicemia. In this study, the incidence of pneumococcal bacteremia was 84% lower in the penicillin group compared with the placebo control group. These findings translated into the inclusion of Phenoxymethylpenicillin (Pen-V) in SCD treatment guidelines. However, the practice of penicillin prophylaxis in SSA is not strongly supported by evidence from the African region, given that recent studies show conflicting results regarding the predominance of *S. pneumoniae* as a cause of bacteremia in SCA [103, 116, 117]. This justifies the need to obtain high-quality evidence regarding the etiology of infection and develop appropriate preventive strategies for bacterial infections in children with SCD living in SSA.

Penicillin chemoprophylaxis should be started as soon as the diagnosis of SCA is made, preferably by 2 months of life [113], because the risk of bacteremia is highest in younger children. However, controversy still exists regarding the ideal timing of discontinuation of penicillin. To date, results of the PROPS II study published in 1995 [118] serve as a benchmark for the widespread practice of stopping prophylaxis after 5 years of life without increasing morbidity. Discontinuation of penicillin prophylaxis can be considered for children aged 5 years and over who have received the PCV13 and PPSV series, received prolonged periods of penicillin prophylaxis, are under regular medical supervision, have no history of severe pneumococcal infection, or have

not had surgical splenectomy [113, 118]. However, penicillin prophylaxis can be continued indefinitely in those with recurrent invasive pneumococcal infections and those who have undergone splenectomy [83].

A major drawback has been the development of antimicrobial-resistant *S. pneumoniae*, but the nasopharyngeal carriage of antibiotic-resistant serotypes seems to have been abated by immunization [113, 118, 119]. Children with SCA should receive routine doses of PCV13, Hib, and meningococcal vaccines administered within a few weeks to a few months after birth. Pneumococcal polysaccharide vaccine (PPSV23) should be administered at 2 years and repeated at 5 years of life [49, 83, 113]. For adequate protection against invasive pneumococcal infections, parents and caregivers should be advised to ensure completion of the vaccine series prior to discontinuation of penicillin prophylaxis at 5 years [83].

**10.4. Chronic Blood Transfusion.** Long-term (chronic) transfusion therapy is recommended in primary and secondary prevention of stroke and is aimed at increasing the oxygen-carrying capacity and the proportion of HbA relative to HbS to prevent or reverse vaso-occlusion-related complications [120]. Approximately 10% of children with HbSS develop overt stroke in the absence of primary prevention [83]. Without monthly blood transfusion, 50% of children with a first stroke experience a second stroke within two years of the initial event [49, 121]. Adams and colleagues [122] demonstrated that the risk of a first stroke in children with abnormal TCD ( $\geq 200$  cm/sec) is reduced by 92% if monthly blood transfusion is provided. Chronic transfusion therapy leads to normalization of TCD velocity in children



with HbSS or HbS $\beta^0$  thalassemia. Results of the STOP 2 trial [123] showed that discontinuation of chronic blood transfusion for prevention of primary stroke in children leads to a high rate of reversal to abnormal TCD blood velocities and risk of stroke.

Blood transfusion can be performed as simple transfusion, manual exchange transfusion, or automated red blood cell transfusion [83, 123]. The advantage of exchange transfusion over simple transfusion is that it reduces HbS level and it results in lower risk of hyperviscosity and lower levels of iron accumulation [120]. Children with acute ischemic stroke should receive EBT with a target Hb of 10 g/dL and HbS <30%. Meanwhile, preoperative simple blood transfusion targets Hb 10 g/dL if general anesthesia is to be used [83]. Individuals receiving regular blood transfusion should have their iron status monitored and iron chelation started using Desferrioxamine (DFO), Deferiprone (DFP), Deferasirox (DFX), or a combination of DFO and DFP when the serum ferritin concentration is  $\geq 1000 \mu\text{g/L}$  or after 10-20 blood transfusions [49, 72]. Another complication of blood transfusion is alloimmunization, which can be minimized by matching donor blood and patient blood not only for ABO antigens, but also performing extended phenotyping for C, E, K, S, and s antigens [46, 83]. Unfortunately, extended phenotyping and screening for alloantibodies are rarely performed in SSA; a region where shortage of packed RBCs and leucocyte-depleted blood is commonly observed [124]. Besides, accurate diagnostic methods for iron overload are lacking, and treatment is costly and not readily available [124].

**10.5. Hydroxyurea.** Hydroxyurea (hydroxycarbamide), a WHO essential medicine [130], is a safe, effective [131], and approved disease-modifying therapy for oral use in children with SCD in sub-Saharan Africa [132]. It has been extensively studied and prescribed in developed countries [131, 133] and yet underutilized in high-SCD-burden countries [134, 135]. In Nigeria, for instance, less than 1 percent of an estimated 1.2 million SCD population use HU [49]. Barriers to HU use range from health system to health providers, patients, and their caregivers (Figure 3) [21, 25, 136–138]. Unless HU is made widely available and multidimensional barriers to its use are addressed, families and patients will continue to experience poor quality of life, high medical costs, increased time out of school due to recurrent and prolonged hospitalization, lost family income, and reduced life expectancy [139].

Although HU leads to increased HbF levels, the actual mode of action is yet to be understood. HU is a ribonucleotide reductase inhibitor and is believed to have multiple mechanisms of action such as stimulation of NO production which has an effect on the vascular endothelium contributing to local vasodilation; decreased expression of adhesion molecules on erythrocytes, white blood cells, and vascular endothelium; reduced hemolysis through improved erythrocyte hydration, and macrocytosis [44, 133, 140]. Just like the baseline HbF level, response to HU therapy also varies among individuals, with only approximately two-thirds of patients with SCD responding to HU [141]. For instance,

individuals with a baseline HbF level between 5% and 10% can have a 2- to 3-fold increase; whereas those with very low baseline HbF can have 10-fold increase on HU [142], implying that some genetic elements in the  $\beta$ -globin cluster predict a response to HU [143]. Ware and associates [144] documented that HbF response is affected by baseline HbF percentage, baseline HbF level, maximum tolerated dose, and treatment adherence.

**10.5.1. Indications for Hydroxyurea in SCD.** Hydroxyurea was first synthesized by Dressler and Stein in 1869, in Germany. It was in the 1960s that its activity against myeloproliferative disorders was discovered [36, 145]. Use of HU for adults with SCD was approved by the United States Food and Drug Administration (FDA) in 1998, and subsequently for children in 2017 [37]. Hydroxyurea is recommended for patients with HbSS and HbS $\beta^0$  thalassemia genotypes but can be considered for other genotypes on an individual basis [37, 127, 146]. It should be noted that indications vary among countries. Consensus guidelines for developed countries such as the United States recommend HU for all patients aged 9 months and above with SCA regardless of clinical severity [83]. British guidelines also recommend HU for infants with HbSS and HbS $\beta^0$ thal aged 9-42 months of life regardless of clinical severity. Children aged >42 months, adolescents, and adults should receive HU if they experience  $\geq 3$  moderate to severe VOC in a year, sickle cell pain that interferes with daily activities and quality of life, and a history of severe and/or recurrent ACS [127]. Countries in SSA, on the other hand, consider specific clinical criteria. For instance, guidelines of high-SCD-burden countries such as Nigeria [49] and Uganda [125] recommend HU in children and adults with abnormal TCD > 200 cm/s, stroke, ACS, > 5 crises per year, 3-4 crises per year, and either a steady-state neutrophil count >  $10 \times 10^9 /\text{L}$  or platelet count >  $500 \times 10^9 /\text{L}$ . Tanzania on the other hand also recommends HU initiation for all children aged at least 9 months with confirmed SCD [105]. Other indications include recurrent priapism and patients with chronic kidney disease who are taking erythropoietin [72, 105]. It is unfortunate that in many instances, HU is started after a child has developed life-changing complications such as stroke.

**10.5.2. Laboratory and Clinical Benefits of Hydroxyurea in SCD.** The earliest clinical trials on the effects of HU on children and adults with SCD were conducted in the early 90s [147, 148]. The beneficial effects of HU manifest after several months of therapy [147]. Hydroxyurea leads to a sustained increase in HbF levels and MCV and reduced WBC, reticulocyte, and platelet counts, and improves erythrocyte deformability and rheology, resulting in reduced vaso-occlusion and increased blood flow [83, 148, 149]. Sickling is inhibited by HbF, which interferes with the polymerization of HbS, because HbF lacks  $\beta$ -globin chains [32]. Individuals with SCD who have high HbF levels have delayed manifestation of symptoms, less severe disease [135], and lower risk of early death [150]. HU also results in increased total hemoglobin levels, reduced vaso-occlusive pain episodes and dactylitis, reduced need for blood transfusion,

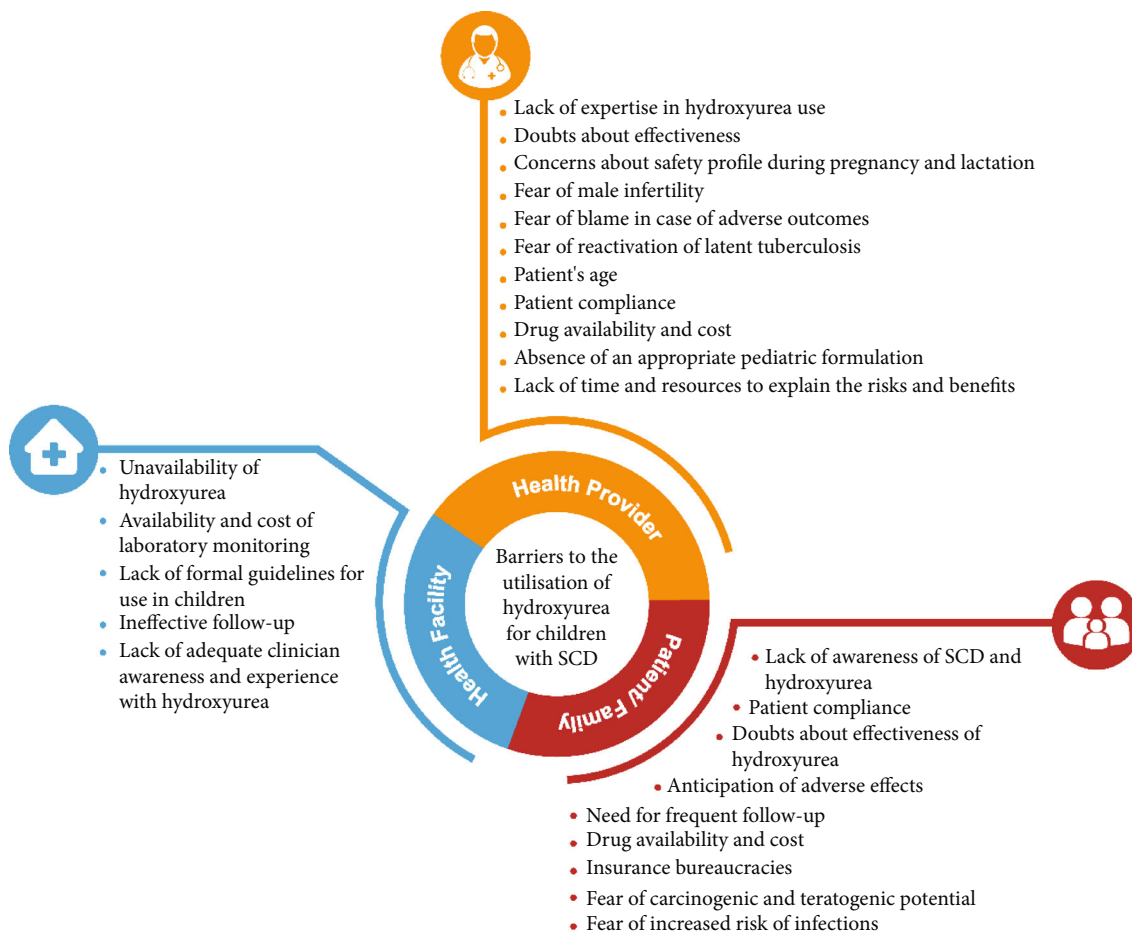


FIGURE 3: Barriers to utilization of hydroxyurea for children with SCD.

reduced hospitalizations and duration of hospitalization, decrease in glomerular hyperfiltration, and death [132, 146, 149, 151]. The Hydroxyurea Safety and Organ Safety (HUSOFT) extension trial [149] revealed a significant decrease in the occurrence of acute chest syndrome. Following four years of HU therapy for children with HbSS and and HbS $\beta^{\circ}$ , 7.5 acute chest syndrome events per 100 person years occurred among patients compared to 24.5 events per 100 person years among controls ( $p = 0.001$ ). The TWiTCH study [152] provided insight that hydroxyurea therapy after at least one year of regular blood transfusion can prevent primary stroke in children with abnormal TCD velocities and without severe vasculopathy as defined by magnetic resonance angiography.

**10.5.3. Adverse Effects of Hydroxyurea.** Hydroxyurea causes decreased white blood cell, reticulocyte, and platelet counts [146, 148, 149, 153]. Fortunately, severe toxicity due to hydroxyurea is rare [154], and these laboratory changes are usually transient and reversible when HU is temporarily stopped [153]. Some children taking HU may experience nausea, diarrhea, and headache, which are often mild [153]. Hydroxyurea is not associated with growth failure [153], and its use in African children is not associated with an increased risk of malaria or bacterial infections [132]. It

is not unusual for clinicians and families to express concerns about the potential for HU to cause malignancy, male infertility, and leg ulcers. There is insufficient or weak evidence that HU is associated with these outcomes [83, 131, 155]. Notably, patients with SCD can spontaneously develop malignancies without HU therapy [156]. Case reports show that children [157] and adults [158] taking HU may develop skin and nail changes in patterns ranging from longitudinal pigmented bands, hyperpigmented nails (melanonychia), palmar creases, and macules. These changes may be observed within 6 to 12 weeks after initiation of HU therapy and at relatively lower doses of HU. They are non-pruritic, painless, and may disappear spontaneously without discontinuation of therapy [157]. Hydroxyurea is also not associated with hepatic and renal dysfunction [133]. More is yet to be learned about the long-term effects of HU in children with SCD, given that HU has only been used for a few decades in this population.

**10.5.4. Contraindications for Hydroxyurea in SCD.** HU should not be administered to pregnant and breastfeeding women, and thus, pregnancy testing should be done for patients in child-bearing age prior to initiation of HU [83]. Women and men taking HU should employ methods of contraception, and when pregnancy is desired, they should

	Barriers	Interventions
Patient/parent	<ul style="list-style-type: none"> <li>• Depression, anxiety, behavioural problems</li> <li>• Academic failure due to lost school days</li> <li>• Cognitive deficits</li> <li>• Perceived lack of disease knowledge by health workers</li> <li>• Inadequate knowledge of current therapy and its benefits</li> <li>• Psychosocial resistance</li> <li>• Lack of knowledge on transition</li> </ul>	<ul style="list-style-type: none"> <li>• Joint pediatric and adult provider SCD clinics</li> <li>• Improve coordination of care between medical teams</li> <li>• Encourage independent visits with the adolescent</li> <li>• Patient interactions with adult-care providers before transfer</li> <li>• Education on transitioning responsibility</li> <li>• Structured and flexible transition plans</li> <li>• Link patients with peers who completed transition</li> <li>• Tours to adult clinics</li> <li>• Prepare for transition in early adolescence</li> <li>• Assess and discuss transition readiness regularly</li> <li>• Employ a transition coordinator</li> <li>• Quality-improvement research</li> <li>• Health-provider training</li> </ul>
Health-system/provider	<ul style="list-style-type: none"> <li>• Inadequate training of primary and subspecialty care providers</li> <li>• Provider biases about opioid use</li> <li>• Inadequate mental health services</li> <li>• Adult health care providers inadequately trained on management of childhood-onset health conditions</li> <li>• Failure of pediatric health care teams to initiate transition and transfer to adult systems</li> <li>• Poor transition coordination and lack of integration of medical records</li> <li>• Poor access to adequate health insurance coverage in young adulthood</li> <li>• Lack of empathy from adult-care providers</li> </ul>	

FIGURE 4: Barriers to adolescent-to-adult care transition and proposed interventions.

discontinue HU at least 3 months before conception [72, 83, 126]. Patients with liver disease, renal disease, and low blood cell counts (absolute neutrophils  $<2,000/\mu\text{L}$ , platelets  $<80,000/\mu\text{L}$ , reticulocytes  $<100,000/\mu\text{L}$ ) should not receive HU [49, 83, 105]. According to some guidelines, HU therapy should not be started if Hb is less than 6g/dl [105]. As such, a complete blood count, reticulocyte count, liver, and renal function test panels should be performed prior to its initiation. ALT should be  $<2$  times the upper limit of normal, and creatinine should be normal prior to starting HU [24]. When possible, HbF levels should be determined using tests such as hemoglobin electrophoresis or HPLC, although elevated HbF level should not deter the initiation of HU [83, 105].

*10.5.5. Prescription, Administration, and Monitoring of Hydroxyurea Therapy in SCD.* Substantial differences in prescription practices exist. It is recommended that clinicians follow guidelines to optimize care and benefits [83]. As a prerequisite, clinicians, patients, and/or family members should hold a discussion about the indications, benefits, and adverse effects of HU, and they should be in a position to be regularly monitored [24].

HU is available as a liquid, capsule, and tablet [159]. Because HU is mostly available as 500mg and/or 250mg capsules in our setting and liquid formulations are not available on a commercial scale [72, 133], open the capsule and dissolve the contents in liquids or foods for infants and younger children [154]. A liquid formulation of HU with a concentration of 100 mg/mL can also be prepared and can be stable for more than 90 days at room temperature [160, 161]. In some countries, 100mg, 200mg, 300mg, and 400mg capsules

of HU are commercially available, which facilitates accurate weight-based dosing [133, 161, 162].

An initial dose of 15 to 20mg/kg/day is prescribed, increased by 2.5 to 5mg/kg/day (maximum daily dose of 35mg/kg) every 8 weeks until a satisfactory clinical response is observed or until a maximum tolerable dose (the dose at which thrombocytopenia, neutropenia, or reticulocytopenia develops), whichever comes first [49, 65, 83]. In situations where only 500 capsules are available, clinicians are advised to calculate the weekly dose of HU in terms of the number of capsules needed per week and distribute the capsules across the week. For example, a 10kg patient initiated on a dose of 20mg/kg/day requires 200mg of HU daily and 1400mg per week. This patient receives three [3] 500mg capsules of HU every week and can therefore take 1 capsule on Monday, Wednesday, and Friday [105].

Perform a complete blood count (CBC) with WBC differential and reticulocyte count 4 weeks after initiation of HU, and 4 weeks after each dose escalation, with the goal of maintaining a neutrophil count of  $\geq 2,000/\mu\text{L}$  and a platelet count of  $\geq 80,000/\mu\text{L}$  [72, 83, 127]. Comparison should always be done between previous and current laboratory values [133]. If neutropenia and thrombocytopenia develop, stop HU therapy and repeat CBC with WBC differential every 1 to 2 weeks. Once blood counts have recovered, restart HU at a dose 5 mg/kg/day lower than that given before the onset of cytopenias [83]. Perform a CBC and reticulocyte count every 2-3 months after determining a stable dose of HU [83, 127]. Patients on HU should have their HbF levels monitored, as well as for adverse effects [49]. However, a failed increase in HbF levels does not indicate a need for discontinuation of HU therapy [83]. Patients

should be advised to continue HU during illness or hospitalization except if neutropenic or bleeding with thrombocytopenia and should not double up doses if a dose is skipped [83, 127].

A trial of a minimum of 6 months on the maximum tolerated dose of HU should be given before consideration for discontinuation, because the optimal clinical and laboratory response to HU may take up to 6 to 12 months. Poor response mainly occurs due to failure of dose escalation or lack of adherence, and to a lesser extent due to frank failure to respond to therapy. In case poor adherence is identified, repeated discussions should be held with families and patients about the benefits of HU therapy, in addition to recognition and rectification of the reasons for poor adherence, because unnecessary dose escalation may result in toxicity and continued nonadherence. Nonresponse to HU is rare in children [133] and should be based on clinical criteria such as failure to reduce the frequency and severity of painful episodes or ACS, rather than laboratory criteria. Long-term HU therapy is indicated if a clinical response is documented, but adherence should be emphasized [83, 127]. A sickle cell expert should be consulted for patients who do not demonstrate a clinical response despite appropriate doses and duration of HU [83].

**10.6. L-glutamine.** Glutamine is an essential amino acid and precursor for the synthesis of glutathione, nicotinamide adenine dinucleotide (NAD), arginine, and nitric acid, which protect erythrocytes from oxidative damage and indirectly maintain vascular tone [33, 163]. L-glutamine (Endari®) was approved by the U.S. FDA in 2017 [164] for use in children aged 5 years and above, 20 years after approval of HU. This approval did not come without contention, given the lack of long-term safety data and the fact that studies have yielded conflicting clinical benefits of glutamine as an antioxidant in many situations [163]. As such, researchers call for more consolidating therapeutic trials to determine the impact of L-glutamine on SCD-associated morbidity and mortality [163]. Data from a phase II randomized, double-blind, placebo-controlled, parallel-group study [165] showed a significant reduction in acute vaso-occlusive pain and hospitalization among patients with HbSS or HbSβ<sup>0</sup>-thalassemia after 6 months of therapy with L-glutamine. In a subsequent phase-3 multicenter double-blind RCT with a 48-week treatment and follow-up period [166], patients aged 5-58 years with HbSS or HbSβ<sup>0</sup>-thalassemia who received L-glutamine (with or without HU) experienced a 25% reduction in acute pain episodes and 33% reduction in hospitalization respectively, compared to placebo (with or without HU). No significant differences were observed with regard to changes in Hb levels, hematocrit, or reticulocyte count, but patients in the L-glutamine arm were more likely to report nausea, chest pain (not of cardiac origin), fatigue, and musculoskeletal pain than the placebo group [166]. Data from this trial was the basis for FDA approval of L-glutamine. A single-center phase-4 trial (NCT04684381) to determine the pharmacokinetic characteristics and safety of L-glutamine in SCD is ongoing and is expected to be completed in 2022 [167]. L-glutamine is an amino acid that

is available as an orally administered powder and capsule for oral suspension or mixing with food. L-glutamine therapy is given twice daily and does not require any monitoring [163, 168]. Major drawbacks include the cost, taste, and lack of biomarkers of response to L-glutamine [36, 163, 169]. Adverse effects of L-glutamine include nausea, fatigue, musculoskeletal pain, and chest pain of noncardiac origin [166].

**10.7. Crizanlizumab.** Crizanlizumab (Adakveo®) is a humanized monoclonal antibody that binds to P-selectin on endothelial cells and platelets and blocks its interaction with P-selectin glycoprotein ligand-1 (PSGL-1), thus preventing cell-to-cell interactions that are involved in the pathogenesis of vaso-occlusion in the microvasculature [170]. Evidence regarding the effect of crizanlizumab for the prevention of vaso-occlusive pain in SCD is encouraging. A double-blind, randomized, placebo-controlled, phase 2 trial involving 198 SCD patients, majority of black race (91.9%), aged 16 to 65 years, was conducted at 60 study sites located in the United States, Brazil, and Jamaica. Patients who had 2 to 10 vaso-occlusive pain crises during the 12 months prior to recruitment were eligible for randomization to high-dose crizanlizumab (5.0 mg/kg), low-dose crizanlizumab (2.5 mg/kg), and placebo groups, with 67, 66, and 65 participants assigned to these categories respectively. Crizanlizumab and placebo were administered intravenously 14 times over a 52-week period, and 129 participants completed the trial. A total of 69 (34.8%) participants exited the study early, 24 in the high-dose crizanlizumab group, 21 in the low-dose crizanlizumab group, and 24 in the placebo group. Patients on hydroxyurea therapy were required to have received it for not less than 6 months, should have been on a stable dose for at least 3 months prior to enrollment, and were not allowed to have any dose alteration during the 52-week treatment phase of the study except for safety reasons. In each group, 25 patients did not receive HU. The median rate of crises per year was 1.63 among patients who received high-dose crizanlizumab, and 2.98 among those who received placebo ( $P=0.01$ ). Patients who received high-dose crizanlizumab had a longer median time to the first crisis compared with placebo (4.07 versus 1.38 months,  $P=0.001$ ). Similar findings were reported regarding the median time to the second crisis (10.32 versus 5.09 months,  $P=0.02$ ). High-dose crizanlizumab resulted in a 62.9% lower median rate of uncomplicated crises per year compared with placebo (1.08 versus 2.91,  $P=0.02$ ). Notably, patients in the crizanlizumab group were less likely to develop events [170]. It is no wonder that in 2019, intravenously administered crizanlizumab received expedited FDA approval as the first targeted therapy for the prevention of VOP in SCD. Crizanlizumab may cause arthralgia, diarrhea, pruritus, vomiting, and chest pain [170].

A phase 2, multicenter open-label trial (NCT03474965) of 100 children aged 6 months to 17 years with any SCD genotype is ongoing [171]. The purpose is to establish the ideal dosing and safety of intravenously administered crizanlizumab in children with or without hydroxyurea.



**10.8. Voxelotor.** Voxelotor (GBT440, Oxbryta®) is a sickle hemoglobin polymerization inhibitor that works by increasing the oxygen affinity of hemoglobin [172]. It is administered as once daily oral tablets or oral suspension. In November 2019, the FDA granted accelerated approval of voxelotor for children and adults aged 12 years and above [173], and later for children aged 4 to 11 years in December 2021 [174]. Marketing authorization of voxelotor for the treatment of SCD in children and adults aged  $\geq 12$  years was granted in the European Union and United Arab Emirates [175]. These decisions followed convincing evidence from the HOPE trial [176], a phase 3, double-blind, randomized, placebo-controlled trial conducted at 60 institutions in 12 countries. Participants were patients with confirmed SCD aged 12 to 65 years whose hemoglobin level was between 5.5 and 10.5 g/dl during screening, and had experienced 1 to 10 vaso-occlusive crises in the past year. In addition, participants who were receiving hydroxyurea were eligible if they were on a stable dose for at least 3 months. Of the 274 participants, 90 were assigned to the 1500mg voxelotor arm, 92 to the 900mg voxelotor arm, and 92 to the placebo arm. At week 24 of follow-up, a hemoglobin rise of more than 1.0 g/dl above baseline was observed in 51% (95% CI: 41-61) of the 1500mg voxelotor arm compared to 7% (95% CI: 1-12) in the placebo arm ( $P < 0.001$ ). One-third (33%, 95% CI, 23-42) of the 900mg voxelotor arm had a significant rise in Hb level at week 24 of follow-up. Hemoglobin levels of at least 10 g/dl at week 24 were observed in 41% of the participants in the 1500mg voxelotor arm, 20% in the 900mg voxelotor arm, and 9% in the placebo arm. The mean rise of Hb was consistent across the voxelotor group regardless of concurrent HU use or baseline Hb. In addition, the incidence of acute anemia episodes (decrease in the Hb level of  $>2.0$  g/dl from baseline during the trial) was lower in the voxelotor arms than in the placebo arm. Participants in the 1500mg voxelotor arm had a significantly higher decrease in indirect bilirubin levels compared to those in the placebo arm, with a mean change of  $-29.1\%$  and  $-3.2\%$  respectively ( $P < 0.001$ ). Similar findings were demonstrated in the phase 2a HOPE KIDS-I trial (NCT02850406) involving 45 children aged 4 to 11 years [177]. Just like L-glutamine and crizanlizumab, voxelotor has not yet been proven to prevent, delay, or improve organ-specific complications (e.g., renal disease, PAH), and improve quality of life or survival [45]. How these drugs can be combined to yield better outcomes is a story for the future.

Currently, a prospective observational study (NCT04930445) of 1000 participants at 45 study sites in the United States is ongoing and is projected to be completed in 2028 [178]. The study intends to evaluate the effect of Oxbryta in children and adults with SCD. In addition, a phase 3 randomized, double-blind placebo-controlled trial dubbed HOPE Kids 2 trial (NCT0421084) involving 224 children aged 2 to 14 years with SCD is underway, with the primary objective of evaluating the effect of voxelotor on TCD measurements [179]. The study is conducted across 43 sites located in the U.S, Europe (United Kingdom, France, Italy), Africa (Nigeria, Ghana, Egypt), and Asia (Saudi Arabia, Oman), and is projected to be completed in 2026.

**10.9. Hematopoietic Stem Cell Transplant.** The first success story of hematopoietic stem cell transplant (HSCT) was published in 1984 [180]. An 8-year-old girl with SCD was cured of acute myeloblastic leukemia after HSCT from an HLA-matched sister with HbAS. The patient was also cured of her SCD complications, showing that SCD can be cured without necessarily reversing to the normal hematological genotype (HbAA).

HSCT is now a well-established cure for SCD that is usually considered for patients with stroke, acute chest syndrome, and recurrent vaso-occlusive pain [181]. Stem cells are usually harvested from the bone marrow, peripheral blood, or cord blood [181]. Although less than 14% of individuals with SCA have HLA-matched siblings as potential donors [46], available data shows that HLA-haploidentical (half-matched) stem cell transplant is a viable alternative, with patients having a 91% overall survival and low transplantation-related toxicity [182], comparable with 92.9% (95% confidence interval: 91.1%-94.6%) overall survival among HLA-matched sibling HSCT [181]. This has been made possible by improvements in conditioning regimens, robust pre- and post-transplantation T-cell depletion, and improvement in supportive care [182].

Wider use of HSCT is limited by limited geographic expertise, availability of human leucocyte antigen- (HLA-) matched donors, and complicated by graft-versus-host disease (GVHD) and death, mostly attributed to infection [84, 181]. Many tertiary facilities in SSA lack infrastructure and funding to perform HSCT. Access to HSCT is limited to 6 of 54 African countries (South Africa, Nigeria, Morocco, Algeria, Tunisia, and Egypt) [183], and patients often seek HSCT in India, Canada, and U.S [184]. Nonetheless, high-burden countries such as Tanzania have accelerated progress in establishing HSCT capabilities through training health professionals both locally and through exchange programs with developed countries; research; establishment of partnerships with community and international organizations and experts in setting up and conducting HSCT; and mobilization of funds [184, 185].

## 11. Other Potential and Futuristic Therapies

**11.1. Pipeline Agents.** Several agents that target HbS polymerization (e.g., Mitapivat, decitabine, Senicapoc), pro-adhesive molecules/selectins (e.g., Rivipansel), and inflammation (e.g., Canakinumab, Regadenoson), among others [46] are either still under study or have been shown to ameliorate SCD severity. Perhaps, some of these agents will translate into SCD care and provide additional benefits.

**11.2. Omega-3 Fatty Acids.** Dietary omega-3 ( $\omega-3$  or n-3) fatty acids, principally docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) are thought to have antioxidant, antithrombotic, and anti-inflammatory properties, and thus likely to modulate key pathophysiologic mechanisms in SCD [186]. These polyunsaturated fatty acids are found in oily fish and fish oil supplements and are substrates for the synthesis of mediators with anti-inflammatory and inflammation-resolving properties called resolvins,

protectins, and eicosanoids [187, 188]. Erythrocyte membranes and plasma of patients with SCD have a high ratio of proinflammatory arachidonic acid (ARA) to DHA and EPA (high  $\omega$ -6/ $\omega$ -3 ratio) compared to controls, a finding which correlates with high sensitive C-reactive protein levels [189, 190]. Arachidonic acid is an  $\omega$ -6 fatty acid that acts as a substrate for the production of eicosanoids that otherwise have inflammatory properties [187, 188].

Few studies have been conducted to establish the role of  $\omega$ -3 fatty acids in ameliorating SCD complications. A small trial of adults ( $n=10$ ) published nearly 20 years ago [191] showed that patients with SCD supplemented with dietary  $\omega$ -3 fatty acids for 1 year experienced a decrease in the frequency of pain episodes requiring hospital care from 7.8 events during the previous year to 3.8 events per year ( $P < 0.01$ ). A single-center randomized, placebo-controlled, double-blind trial [192] conducted in South Sudan involving 140 patients aged 2 to 24 years with SCA found that  $\omega$ -3 fatty acids reduce the median rate of vaso-occlusive pain episodes from 4.6 to 2.7 per year ( $P < 0.01$ ) and of pain requiring hospitalization from 1 to 0 per year ( $P < 0.0001$ ). The annual frequency of severe anemia was also reduced from 16.4% to 3.2% ( $P < 0.05$ ), whereas that of transfusion reduced from 16.4% to 4.5% ( $P < 0.03$ ). Although this data provides insight regarding the potential benefits of  $\omega$ -3 fatty acids in SCD, there is a need for a stronger body of evidence through a carefully planned and larger multicenter trial.

**11.3. Gene Therapy.** Gene therapy is a relatively new and rapidly developing science with both curative and disease-modifying potential for SCD. It was born out of an improved understanding of the molecular pathways that regulate erythropoiesis and globin switching in mammals, and improved gene transfer tools. Gene therapy broadly takes a variety of approaches including addition of a helpful gene, often using a lentiviral vector, gene knockdown (e.g., BCL11A silencing), direct globin gene editing to rectify the mutation (changing the HbS-encoding gene to HbA-encoding gene), and gene editing of elements that regulate globin, to at least partially reverse the normal hemoglobin switching from HbF to HbA (e.g., by targeting the BCL11A gene) [193, 194]. Recently published pilot studies have shown that single treatment using gene therapy techniques results in sustained production of HbA in most RBCs and increased total Hb and HbF levels, reduces hemolysis, and completely resolves severe vaso-occlusive events [195, 196], whereas variable findings have been documented in other studies [197, 198]. Several other pilot studies are underway to primarily assess the feasibility, safety, and efficacy of gene therapy in patients with severe SCD [198–200].

A recent trial of two patients (19 year-old with transfusion dependent thalassemia and 33 year-old with HbSS and a single  $\alpha$ -globin deletion) showed that infusion of autologous CRISPR-Cas9-edited CD34+ hematopoietic stem and progenitor cells resulted in an early, significant, and sustained increase in total Hb and HbF levels, reduction in intracellular HbS levels, elimination of transfusion requirement, and acute vaso-occlusive pain episodes [201]. Sepsis and pneumonia were reported to occur in the pres-

ence of neutropenia, in addition to cholelithiasis, veno-occlusive liver disease with sinusoidal obstruction syndrome, and abdominal pain [201]. This revolutionary precision-based technology is still in experimental stages and will not be available anytime soon in low- and middle-income countries.

## 12. Adolescent to Adult Care Transition

Programs that support the transition and integration of adolescents with SCD into adult-centered care are crucial, given that the life span of individuals with SCD continues to increase. Transition of adolescents into adult-centered care for SCD usually occurs at  $\geq 18$  years, but preparation for readiness to transition should begin a few years earlier [202, 203]. Patients aged 18 to 25 years can be reviewed by the pediatric and adult care hematologist and progressively bridged to only adult care by 26 years. However, it has been observed that adolescents and young adults with SCD experience increasing severity of complications, hospitalization, and mortality, particularly between 15 and 34 years, a period during which transition occurs [202, 204]. Furthermore, adolescents and young adults experience inadequate care in the emergency room and prefer their usual care physician, which compromises transition outcomes [205]. Ineffective transition is attributed to several patient, parent, health provider, and health system barriers. These barriers and potential interventions are summarized in Figure 4 [203, 205–207]. Perhaps, adult care providers should foster good relationships with patients, develop expertise to coordinate, and maintain optimal quality of care during and after transition, as well as develop tools to monitor the outcomes of transition.

For a healthcare transition program to be effective, it should be well structured and systematic. More precisely, a transition program comprises of six core elements, namely, (1) developing of a transition policy, (2) tracking and monitoring progress, (3) assessing transition readiness, (4) planning for adult care, (5) transfer to adult care, and (6) integrating into adult care [208]. While transition programs have been prioritized in high-income countries where individuals with SCD live for an average of 60 years [207], many countries and hospitals in SSA lack structured transition programs, and adult hematologists and nurses experienced in child-onset chronic illnesses are exceedingly rare. As such, individuals who survive into adulthood continue to attend pediatric SCD clinics and inpatient care provided by nurses, medical clinical officers, and general practitioners without an extensive understanding of the complexity of SCD complications in adults. There is no doubt that pragmatic trials are urgently needed to establish feasible approaches that facilitate readiness for a smooth transition to adult care in high-SCD-burden countries in SSA [206], and yet still maintain good quality of care and outcomes of adolescents and adults with SCD. Although this may be a highly complex matter, given the numerous health system challenges, we believe that continued research and patient/family inclusive quality improvement initiatives and development of quality indicators for transition readiness and successful transition [209]

will be key in fostering success. However, we need to first optimize the collaboration between pediatric and adult care providers including medical doctors (general practitioners and specialists), clinical officers, and nurses. Besides, the concept of care transition of patients with chronic life-debilitating illnesses should be embedded in the curricula of undergraduate and postgraduate medical and nursing training institutions in SSA.

### 13. Prevention of SCD

Key approaches to the prevention of SCD include universal newborn screening, premarital and preconceptional genetic counselling and testing. Achieving this requires extensive community sensitization, availability, and accessibility to free or subsidized SCD screening services, which requires the involvement of key stakeholders such as religious, cultural, and political leaders, and village health teams [24].

### 14. Conclusion

Sickle cell disease is one of the most common monogenic diseases worldwide and is highly prevalent in SSA. It had been largely neglected as a global health priority until 2006 when the World Health Organization recognized it as a global health priority. More than 500 children die every day because of delayed diagnosis and lack of comprehensive care for SCD [15]. Implementation of newborn screening in sub-Saharan Africa is still in infancy, and yet, early diagnosis facilitates early enrolment into comprehensive care programs and family health education, hence reducing the morbidity and mortality associated with SCD. There is no doubt that this can be widely achieved through the use of POCTs, which are considerably cost-effective and accurate options for early screening of SCD in newborns. Their use should be integrated into existing preventive care programs such as immunization and HIV early infant diagnosis in high-burden countries in SSA [15]. Additionally, there is an urgent need to implement the widescale use of hydroxyurea in combination with other approved disease-modifying therapies (L-glutamine, crizanlizumab, voxelotor) for children with SCD in SSA. Since curative therapies (HSCT and gene therapy) are distant options for the majority of Africa's children with SCD, countries should improve the access and quality of comprehensive care. To further enhance the survival and quality of life of patients with SCD, countries in SSA should invest in health systems research to streamline the transition from adolescent-to-adult care.

### Abbreviations

Hb:	Hemoglobin
HPFH:	Hereditary persistence of fetal hemoglobin
HU:	Hydroxyurea
NBS:	Newborn screening
POCT:	Point-of-care test
RBC:	Red blood cell
SSA:	Sickle cell anemia
SCD:	Sickle cell disease

SCT:	Sickle cell trait
SSA:	Sub-Saharan Africa.

### Data Availability

All material supporting the conclusion of this review has been included within the article.

### Conflicts of Interest

The authors declare no competing financial interests or personal relationships that could have appeared to influence what is reported in this paper.

### Authors' Contributions

WIE conceptualized the research and drafted the manuscript. GN, WMW, MT, EA, GK, SO, PKK, SA, and DA reviewed and improved the manuscript. All authors approved the final manuscript.

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