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Sickle Cell Disease: a malady beyond a hemoglobin defect in cerebrovascular disease

Junaid Ansari[1], **Youmna E. Moufarrej**[2], **Rafal Pawlinski**[3], and **Felicity N.E. Gavins**[1]

[1]Department of Molecular and Cellular Physiology, Louisiana State University Health Sciences Center - Shreveport, Shreveport, Louisiana, USA

[2]Louisiana State University School of Medicine - Shreveport, Shreveport, Louisiana, USA

[3]Department of Medicine, University of North Carolina Chapel Hill, North Carolina, USA

Abstract

Introduction—Sickle cell disease (SCD) is a devastating monogenic disorder that presents as a multisystem illness and affects approximately 100,000 individuals in the United States alone. SCD management largely focuses on primary prevention, symptomatic treatment and targeting of hemoglobin polymerization and red blood cell sickling.

Areas covered—This review will discuss the progress of SCD over the last few decades, highlighting some of the clinical (mainly cerebrovascular) and psychosocial challenges of SCD in the United States. In addition, focus will also be made on the evolving science and management of this inherited disease.

Expert Commentary—Until recently hydroxyurea (HU) has been the only FDA approved therapy for SCD. However, advancing understanding of SCD pathophysiology has led to multiple clinical trials targeting SCD related thrombo-inflammation, abnormal endothelial biology, increased oxidant stress and sickle cell mutation. Yet, despite advancing understanding, available therapies are limited. SCD also imposes great psychosocial challenges for the individual and the affected community, which has previously been under-recognized. This has created a pressing need for complementary adjuvant therapies with repurposed and novel drugs, in addition to the establishment of comprehensive clinics focusing on both the medical treatment and the psychosocial issues associated with SCD.

Keywords

Sickle Cell Disease; hydroxyurea; stroke; thrombosis; neutrophils

Corresponding author: Felicity N. E. Gavins, Department of Molecular and Cellular Physiology, LSU Health Sciences Center – Shreveport, 1501 Kings Highway, LA 71103, Shreveport, USA. fgavin@lsuhsc.edu.

Declaration of interest

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1. Introduction

Sickle cell disease (SCD) is a common hereditary hemoglobinopathy caused by a single gene mutation with a protean course. The disease itself was first reported by Herrick in 1910 [1], with the molecular defect being discovered by Pauling and Itano in 1949 [2] and further described and characterized by Ingram [3] almost six decades ago. Despite the known nature of the disease, progress in the science and the overall management has been a relatively slow process. The recent advent of new therapeutic targets [4,5], use of gene therapy [6], and excellent success rate of HLA-identical sibling transplantation [7] have brought new hope to the scientific and affected communities.

2. Epidemiology

2.1. Origin and distribution of sickle hemoglobin (HbS)

The persistence of SCD arose in areas of equatorial Africa and Asia with high endemicity of *Plasmodium falciparum*, the protist responsible for causing malaria. This is due to the evolution of the balanced polymorphism, which offers selective advantage to heterozygotes with the HbAS mutation (sickle cell trait). Carriers of the HbAS gene are estimated to be protected from developing severe malarial symptoms by 90% [8], but patients with homozygous mutations (HbSS) have worse outcomes and may develop lethal complications of malaria [9].

Global migration has increased carriers of the HbS mutation from 1.6 million to over 2.6 million individuals worldwide since 1940 [10]. The Benin haplotype, which entered the United States (US) gene pool through slave trading with West and Central Africa, is the predominant haplotype in the US [11] and worldwide today [12].

2.2. United States (US)

It has been estimated 70,000–100,000 people in the US alone are affected by SCD, with an additional three million possessing the sickle cell trait [13]. A 2010 US census analysis study revealed that 89,079 people in the US have SCD, of which 80,151 self-identified as African American [14]. It has also been estimated between the years 1999 and 2007 more than 197,000 annual hospital visits were related to SCD [15]. In addition, in 2014 a study by Ojodu et al., revealed that, in the 44 US states included in the study, 1.5% of all newborns screened were positive for HbS, with Mississippi having the highest rate at 3.4% (Figure 1) [16]. It is known that economically poorer states, such as Mississippi, where SCD is more prevalent, often have limited access to appropriate care facilities [16,17]. In the US, despite SCD patients surviving into adulthood, the current average age of death is forty years old [14], with this value being significantly lower in males. In 2005 the age of death was estimated to be 33.4 years for SCD males and 36.9 years for SCD females [16]. Importantly, widespread clinical use hydroxyurea (HU) has increased the survival for SCD patients [18], coupled with blood transfusion and bone marrow transplantation [19]. However, this increase survival has lead to heightened clinical and psychological challenges associated with adult SCD (as outlined below).

3. Milestones

The “sickle” phenotype of erythrocytes, now known to be attributed to SCD, was first described in 1910 by Herrick. Sickling was later identified as occurring in decreased oxygen conditions, during which hemoglobin structure is altered. In 1949, Pauling et al. identified it as a molecular disease, noting that the hemoglobin of SCD individuals differed from that of healthy individuals in electrophoretic motilities. Ingram proceeded shortly thereafter with the discovery of this difference at the amino acid level, indicating a genetic role in the disease.

HU was first synthesized in 1869 [20] and in 1984 drug testing on anemic monkeys proved its ability to induce fetal hemoglobin production [21]. Shortly thereafter, HU was tested on SCD patients and produced similar beneficial results [22] and in 1998 HU was approved by the FDA for treatment of SCD.

In 2006, the World Health Organization (WHO) recognized SCD as a global health crisis and urged countries in which SCD is prevalent to design and enforce SCD screening and support programs as well as train additional health care providers, implement educational programs and provide adequate access to emergency care for SCD. In 2008, June 19th was designated as World SC Day by the United Nations in hopes of increasing awareness of the most common genetic disease worldwide [23].

Screenings for HbS gene mutations in newborns was first implemented across the US in January 2006 [16]. However, SCD confirmatory testing can be expensive and requires specialized equipment, which is mostly unavailable in underdeveloped countries such as those in Africa where SCD is most prevalent (affecting up to 25% of the population) [24]. SCD screening tools are essential in order to provide adequate and early preventative care for the devastating complications of SCD e.g. stroke, which is far more common in SCD than in the general population. As many as 25% of SCD children (≤six years of age) [25] accumulate ‘silent strokes’ at a rate that increases to 39% by the time these children reach adulthood (≥18 years of age) [26]. Furthermore 11% of SCD patients will have had at least one stroke by the time they are twenty years of age, increasing to 24% by the time they are forty-five years old [27,28].

Recent technological improvements have led to the development of a smartphone attachment called “SC Tester,” which under deoxygenated conditions can screen for sickled red blood cells (sRBCs) in a blood sample at a low cost [29]. In addition, the use of smartphones with medical applications has been shown to potentially lead to better treatment compliance especially in adolescent and young SCD patients [30]. Due to the fact that early intervention is essential for effective life-long SCD management, mobile devices like these could accelerate the future of rapid screening programs in underdeveloped countries and subsequently decrease the cost of SCD care. For example, implementing a SCD screening program for pregnant women in Benin resulted in 85.2% of newborns with SCD being enrolled in a follow-up care program, which consequently decreased mortality rate in children under five years old by 10% [31]. Pneumococcal vaccination and penicillin prophylaxis have additionally reduced the risk of mortality for SCD children by preventing

infection [32]. Some of the important milestones in the history of SCD are included in Figure 2.

4. Hydroxyurea (HU)

HU reduces incidences of pain and (ACS) chest syndrome in patients as well as decreasing the number of transfusions needed, thereby decreasing hospitalization of patients (BABY HUG trial) [33,34]. By increasing HbF levels, HU increases the overall survival of SCD patients [18] and decreases morbidity and mortality secondary to vaso-occlusive (VOC) events [35], cerebrovascular events [36,37], and proteinuria [38]. Children (≤18 years old) treated with HU have been shown to exhibit a more robust response to HbF induction than adults [39], possibly reflecting their greater capacity to reactivate HbF programing and justifying early intervention with HU as central to effective life-long SCD treatment.

Although HU has been proven to be beneficial for SCD patients it is still administered to <25% of adult SCD patients [40,41]. This clinical ‘disconnect’ has been attributed to many factors at the patient, caregiver, and provider levels. Some of the common barriers to HU treatment are lack of knowledge, misperception about HU’s disease modifying efficacy and concerns about its ‘experimental’ nature, as well as short and long term effects of HU including risks for cancer, birth defects and infertility [42]. In consideration of these issues, healthcare experts now argue for the use of HU both in pediatric and adult population [43]. In a recent clinical trial (TWiTCH study) comparing HU with chronic transfusion, high-risk children with SCD maintained their TCD velocities with no new cerebral infarcts in either treatment group. This study provided evidence to suggest that HU efficacy helps prevent stroke in the pediatric population [37].

5. L-glutamine

The FDA recently approved L-glutamine oral powder to reduce the acute complications of sickle cell disease in adult and pediatric patients (five years and older) on July 7th 2017 [5]. The research on L-glutamine as a potential disease modifying therapy in SCD has been progressing for some time. One of the earliest studies was performed in 1998, where seven adult sickle cell anemia patients, who took 10 grams of pure L-glutamine, showed subjective improvement in the pain levels [44]. In 2014 the same group did a Phase III study on 230 patients (152 were assigned L-glutamine and 78 placebo). Patients on L-glutamine showed significant reduction in the painful crises and hospitalization (NCT01179217). The rationale behind using L-glutamine is based on the fact that sickle RBCs have low nicotinamide adenine dinucleotide (NAD) and glutamine is a precursor of NAD, hence supplementation will counter the oxidant-dependent pathophysiology of sickle RBC [5,44–46]. Arginine is another anti-oxidant candidate, which has shown significant promise in the management of complications associated with SCD. Arginine therapy resulted in promotion in the healing of long standing refractory ulcers and significant reduction in pain episodes in SCD patients [47,48]. Furthermore, Glutamine is an arginine prodrug which may also explain some of the benefits of these types of therapies [46].

6. Clinical challenges

As stated above, SCD is one of the most common causes of early onset stroke, especially in African Americans. Multiple factors play a role including: chronic hemolytic anemia, hypoxia, VOC events, and vascular endothelial dysfunction [27,49–52]. These factors lead to further complications including silent cerebral infarcts (SCI), transient ischemic attacks (TIA), overt ischemic strokes (IS), and hemorrhagic strokes (HS). Stroke risk is 333 times higher in SCD vs. non-SCD pediatric population [27,28].

SCI are the most common neurologic injuries associated with SCD in children, increasing their subsequent stroke risk [53] and neurocognitive deficits [51,54]. These risks accumulate and become more apparent with age. Neurocognitive deficits remain the most challenging and under-diagnosed condition associated with SCD and contributes to higher morbidity and mortality in SCD sufferers [54].

IS in SCD patients display a bimodal presentation: common in early childhood and in the elderly. These types of strokes are managed by emergency exchange transfusion to reduce HbS to less than 30% [36]. The use of thrombolytics, anti-coagulants and anti-platelet therapies is limited due to less data, inadequate systemic experience, and absence of well-designed studies [36,55]. HS on the other hand are more common in individuals between 20–29 years of age and associated with higher mortality and morbidity compared to the risk for IS [56]. In the case of HS, the goal is to stop the bleeding by neurosurgical intervention or by discontinuing the cause (e.g. anticoagulant, anti-platelet therapy) [36]. Exchange blood transfusions are the main component of primary stroke prophylaxis, and recent evidence suggests that HU may also be effective in preventing stroke-related complications [37,57,58]

Cardiopulmonary complications are also one of the leading causes of death in SCD [59–62] and include a wide range of problems such as ACS, pulmonary hypertension (PH), asthma, cor pulmonale, and cardiac ischemia [49,59,63]. ACS is the second most common cause of hospitalization in SCD patients and a major cause of SCD-related mortality [59,64]. ACS in SCD has a distinctive manifestation with pneumonia-like symptoms characterized by chest pain, fever, tachypnea, cough, and arterial oxygen desaturation and can mimic other cardiopulmonary abnormalities which pose a diagnostic challenge [65]. Routine treatments for ACS include hydration, bronchodilation, incentive spirometry, empirical antimicrobial therapy, and supplemental oxygen [65]. Opioids are often needed to manage pain. If the condition deteriorates, typically blood transfusions are needed. Asthma is associated with ACS and pain in children with SCD, which can lead to increased mortality in pediatric as well as in adult SCD populations and should be managed aggressively [66–69].

PH affects approximately 10% of adult SCD patients and may go undetected until advanced stages of SCD exist [70]. The PUSH study (Pulmonary hypertension and the Hypoxic Response in SCD) determined the role of various risk factors in the development of PH. This study concluded that the frequent severe pain episodes is an independent risk factor in addition to other risk factors such as asthma in the pathogenesis of PH and ACS in SCD and should be considered for risk stratification [68]. Symptomatic PH is mainly managed by optimization of HU, exchange transfusions, anticoagulation, and PDE (phosphodiesterease)

inhibitors and endothelin antagonists [70]. The new guidelines laid down by the American Thoracic Society gives more comprehensive details about the management of pulmonary complications in SCD and recommends: 1) use of HU in patients with high mortality risk; 2) indefinite use of anticoagulant therapy in patients with confirmed PH and venous thromboembolism; 3) Targeted PH therapies (PDE and endothelin inhibitors) should be used only in selective patients [71].

Vaso-occlusive pain is the most common cause of acute morbidity in SCD characterized by recurrent, self limiting excruciating episodes which can develop almost anywhere in the body lasting between few hours to two weeks [72]. These pain crises often result in frequent hospitalizations and have been associated with reduced survival and end organ damage. The management of sickle cell related pain is often individualized and should be based on the degree of pain. Early, adequate and aggressive management consisting of opioid therapy is a reasonable strategy and any delay in treatment may have unwanted consequences [73].

Overall, there has unfortunately been a “negative attitude” towards management of pain in SCD patients. These negative attitudes toward patients with painful sickle crises have been compounded by racial stereotypes, the effects of the disease in limiting educational and employment opportunities, suboptimal medical coverage, and the large doses of opioids often required to obtain pain relief [74]. As such, the association of sickle cell pain management and opioid addiction has been overestimated. Recent studies and surveys are beginning to debunk these prevailing notions and have suggested that these patients should be given adequate pain therapy and management [75,76]. It is important to recognize and take note of the fact that chronic opioid therapy in SCD patients might also lead to rapid tolerance and central sensitization, resulting in increased pain and overall disease burden and lower QoL [77].

7. Psychosocial challenges

Nearly a decade ago, it was reported that for pediatric patients, SCD costs were estimated to be $11,075 (with Medicaid) or $14,772 (without Medicaid) per year due to hospitalizations and other medical expenses [78]. Costs were even higher in adult patients with an average of $34,266 per year due to the chronic nature of the disease and potential end organ damage [79]. HU has been estimated to decrease this financial burden for SCD treatment by at least 20%, making it cost-effective, with the health benefits far out weighing the risks [80]. However, since these reports came out, costs and resource utilization has only increased and as such, these figures are now likely to be far greater.

Anxiety and depression are anecdotally known to be common in SCD patients. Quality of life (QoL: a measure of a patient’s overall satisfaction and happiness with their life) in SCD patients who experienced increased pain episodes was significantly decreased and associated with symptoms of depression. Health related quality of life (HRQL), which describes the effect of a disease on an individual’s overall well-being, is also lower in these patients [81].

The pain associated with SCD and the necessity for frequent hospitalizations greatly complicates job employment. The great financial burdens of SCD create further economic

problems. Due to their physical limitations, children may be ostracized in school, leading to social anxiety at school or later in life. This is a bigger challenge for adults who may face similar experiences at their educational institutions or work places. The use of cognitive behavioral therapy (CBT) for SCD patients has been proven to relieve symptoms of anxiety and depression and improved their quality of life scores [82].

8. Comprehensive SCD Centers (CC)

CCs focus on life-long SCD management usually run by lead physicians trained in SCD healthcare and supported by other health care staff and social workers. The centers often include specialized services necessary to the SCD patient, such as access to blood banks for transfusions [83,84]. Currently, there are over forty CCs in the US. However, low-income states (e.g. Mississippi and Louisiana) and countries (e.g. Africa) which have higher numbers of SCD patients have fewer or no CCs [85]. A study has shown that family physicians feel incapable of providing proper treatment and support for SCD patients and these CCs are designed to implement proper care, specific to SCD patients [86]. It is important to note that whilst an increase in the number of CC's and proper training for family physicians and healthcare providers is essential, there also needs to be considerable efforts made in helping those patients which live in very remote areas gain access to CCs and proper healthcare.

9. Mitigation strategies

SCD poses immense challenges to the globally affected population with multiple factors needing to be considered and worked upon on a personal, community, state, and national and international level that could lead to better life amongst the SCD population. The most important measures include: the establishment of SCD CCs; widespread use of HU and development of other disease-modifying agents targeting sickling phenomenon as well as other pathobiologically relevant targets such as the recently approved L-glutamine [5]; early identification and management of the psychosocial impact of the disease; and development of support groups and financial programs for those with the disease. Some of the strategies have been listed in Table 1.

10. Scientific strategies and progress

Despite the long history and global burden of SCD, treatment options are still very limited with focus being on the preventive and the symptomatic aspect of the disease, rather than on disease modification. SCD is now recognized as not merely an Hb disorder, but a systemic disease, which causes widespread tissue/organ injury, including endothelial and inflammatory (e.g. neutrophils) dysfunction and coagulation/thrombosis abnormalities [87,88]. These factors all contribute to the hypercoagulable state of SCD.

Many of these complications are caused by abnormal endothelial function. The exposure of endothelium to abnormal sRBCs results in enhanced angiogenic activity and hypercoagulation with altered vasoregulation. There is additionally an increase in adhesion and inflammatory markers. Heme release leads to plasma nitric oxide (NO) depletion, which

dramatically alters many homeostatic mechanisms and results in powerful VOC, decreased blood flow, platelet activation, and neutrophil recruitment [89,90]. As such, SCD pathobiology and hypercoagulable state is also a consequence of ischemia reperfusion (I/R) phenomenon [91].

11. Inflammation and coagulation/thrombosis cross-talk in SCD

Inflammation shifts the hemostatic mechanisms in favor of coagulation/thrombosis [92] in multiple diseases including SCD. The hypercoagulation state is a prominent feature of SCD and is mediated by activation of both intrinsic (involving FXIIa and FXIa and amplification of FXa generation) and extrinsic (involving the transmembrane receptor tissue factor (TF) and plasma factor VII/VIIa (FVII/FVIIa)) coagulation pathways [93,94]. In addition, SCD patients exhibit increased plasma markers of thrombin generation, such as prothrombin fragment 1.2 (F1.2) and thrombin anti-thrombin (TAT) complexes [95], and increased D-dimer (a marker of increased fibrinolysis) and increased circulating fibrinogen, von Willebrand factor (vWF) [50] and decreased protein C and S levels [96]. We previously investigated the role of some of these factors in SCD mice using genetic and pharmacological methods. We found that TF inhibition attenuates thrombosis in both cerebral arterioles and venules [50]. In addition, immunologic or genetic interventions targeting endothelial protein C receptor (EPCR), activated protein C (APC), or thrombin also blunted the enhanced microvascular thrombosis [50]. Furthermore, microparticles (MPs) derived from RBCs and platelets may also influence SCD pathobiology especially maintaining its hypercoagulable state through activation of FXI dependent coagulation pathways [97].

Although SCD is a hypercoagulable disease, very few clinical trials evaluating the effect of antiplatelet agents (e.g. aspirin and ticlopidine) and anti-coagulant agents (e.g. heparin and warfarin) have taken place and those that have were unconvincing and associated with major bleeding complications at doses tested [98,99]. However, there is growing interest in targeting FXII and FXI to prevent thrombosis without the added bleeding complications. A recent Phase 2 trial using antisense oligonucleotide to reduce FXI mRNA showed reduced thrombotic events and bleeding in patients undergoing knee replacement surgery [100]. It remains to be seen if this strategy is successful in SCD.

12. Cellular cross-talk and role of neutrophils in SCD

Multiple cell types have been implicated in the pathogenesis of SCD [101]. Neutrophils in particular have generated much interest in perpetuating the overall vascular pathology of SCD [101] and positively correlate with morbidity and mortality associated with the disease [102,103]. SCD neutrophils are hyper-adhesive to the vascular endothelium as well as to other cell types with excessive binding interactions in SCD producing an abnormal and highly-activated cellular environment. They are larger and less deformable than RBCs thereby impeding the passage of RBCs and other leukocytes, particularly in capillaries, increasing the risk for VOC. Activated platelets “piggyback” onto neutrophils and bind with the endothelium. Upon activation, neutrophils release their extracellular traps (NETs). These chromatin structures form tangles of extracellular fibers that bind with sickled RBCs and

platelets, forming multicellular complexes and provoking VOC [90,103]. We were the first to show neutrophils are responsible for an accelerated thrombus formation within the cerebral microvessels of mice with SCD [50]. Figure 3 illustrates neutrophil biology in SCD.

13. Other Strategies

The considerable paradigm shift in our understanding of SCD has led to multiple clinical trials targeting different mechanistic aspects of the disease pathobiology [40,101]. Many of these trials are focused on the anti-switching mechanism (induction of HbF); others have targeted the endothelial surface, reactive oxygen species (ROS), and neutrophil entrapment. In a recent double-blind, randomized, placebo-controlled Phase II trial, patients receiving crizanlizumab had a significantly lower rate of sickle cell-related pain crises than placebo [4].

Gene therapy and gene editing strategies have also been employed for the management of SCD over the last three decades. With the recent advent of CRISPR-Cas9 (Clustered regularly interspaced short palindromic repeats) and TALEN (Transcription activator-like effector nucleases) gene editing tools, safe and efficient gene transfer with stable gene expression is a potentially achievable goal [104,105]. Ribeil et al. recently reported successful gene therapy using a lentiviral vector-mediated addition of a β-globin gene in a fifteen year old boy with SCD [6].

Hematopoietic stem cell transplantation (HSCT) provides a definitive cure for SCD and has been used in CCs [106]. However, the potential morbidity and mortality associated with HSCT, insignificant overall survival and disease free-survival when compared to patients treated symptomatically, coupled with high cost of HSCT, have led to its underuse [107]. A recent international survey done by Gluckman et al. reported excellent long-term survival in patients with HLA (Human leukocyte antigen)-identical sibling transplantation [7], but lack of healthy HLA-matched siblings makes it a significant challenge. However, the evolution of partially myeloablative conditioning regimens and haploidentical HSCT may allow more widespread use of this modality in the near future and increase the donor pool [108]. These varied new targets may help develop effective combinational approaches for managing acute complications e.g. ACS, pain crisis and cerebrovascular complications e.g. stroke. Some of the evolving therapeutic approaches in SCD are included in Table 2.

14. The future of SCD: Challenges and opportunities

SCD remains a devastating chronic and lifelong condition posing multiple challenges to the affected population (Table 3). The evolution of SCD etiopathogenesis has brought hope to this long recognized, yet poorly understood and understudied disease. Furthermore, universal screening of newborns and prophylactic use of antibiotics has improved child survival, and HU, blood transfusion and more recently bone marrow transfusion has increased the overall lifespan and QoL of these patients. However, it is imperative that the health care community acknowledge that SCD has important long-term psychological and social consequences that can significantly hamper socioeconomics and QoL issues for SCD patients and their families. Establishing more CCs, training more physicians in SCD

specialty and improving community support may mitigate many negative factors. Prospective trials using HU with other disease modifying agents and approaches such as gene therapy and gene editing tools like CRISPR may modify the disease process by influencing the abundance of HbS and modifying the surrounding milieu. Until gene therapies are optimized, HU-based therapies alone and in combination with approaches targeting different SCD mechanisms remain the best approach for SCD therapy.

15. Expert Commentary

SCD was discovered over a century ago (in 1910), but the development and understanding of the disease has been relatively a gradual process. SCD is common in African Americans with one out of every 365 people inheriting and is responsible for approximately 113,000 hospitalizations and $488 million dollars in costs annually in United States [109,110]. The disease has a huge impact on the patient's quality of life (QoL) and poses chronic physical and psychosocial challenges to the affected community with far bearing consequences to the patient. There has been a vast improvement in the overall life expectancy and QoL of SCD patients over the past few decades. These improvements are due to efforts such as universal screening, vaccination and antibiotic prophylaxis, and advent of HU therapy, however further efforts are still needed.

Advancement in the understanding of the pathophysiology of SCD has led to a number of research and clinical projects, and resulted in development of therapeutic targets including anti-inflammatory, anti-oxidant and anti-coagulant agents (Table 2). Recent success of the L-glutamine, crizanlizumab and gene therapy has brought more impetus to the scientific community. L-glutamine, which is an anti-oxidant, is the second drug to receive FDA approval for SCD adult patients and the only FDA approved drug for pediatric patients. These advancements, alongside strong research efforts such as our own which looks into inflammatory (e.g. neutrophil-platelet interactions) as well as coagulation/thrombotic pathways in SCD, will hopefully result in the development of better disease modifying therapies.

Another huge challenge associated with the disease has been a psychosocial one. SCD patients are more vulnerable to neglect due to certain social and racial stereotypes and lack of economic support. This should be addressed by widespread social awareness so that SCD patients are looked upon with utmost care and compassion. We also need development of better models of care such as CCs, and patient/family centered medical homes especially in the economically challenged and more prevalent regions e.g. in the states of Louisiana and Mississippi and countries e.g. Africa.

In the coming years the future of SCD looks more promising and hopeful, with patients having more therapeutic options tailored to individual cases (precision medicine), better social support and more research and development. Our research efforts looking into SCD as a thrombo-inflammatory disease model may be able to attenuate some of the maladaptive cellular interactions and achieve a much healthier SCD phenotype resulting in fewer complications (e.g. ischemic stroke) and reduction in morbidity and mortality associated with the disease.

16. Five-year view

The considerable shift in the understanding of SCD has led to a variety of scientific advances in the field. The recent success with various trials (crizanlizumab, L-glutamine, GBT440, Prasugrel) [4,5] have given more hope to the affected community and will probably change the current treatment paradigms, offering a more optimized treatment to patients. In addition to this progress, the recent use of genetic approaches such as gene therapy and gene editing tools e.g. CRISPR, and reports of excellent long-term results of HSCT will be key milestones in the therapeutic progress of this disease.

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Key Issues

- SCD is the most common congenital hemoglobinopathy, affecting almost 100,000 individuals in the US alone.
- The chronic nature of SCD has an enormous socioeconomic impact on affected communities, and SCD patients live in a state of continuous physical and psychological disability.
- In the past, management has focused mainly on primary prevention and symptomatic relief. Hydroxyurea (HU) and the recently developed L-glutamine are currently the only two Food and Drug Administration (FDA) approved disease-modifying drugs available.
- There is a pressing need for complementary adjuvant therapies with repurposed and novel drugs, as well as establishment of more comprehensive SCD centers focusing on the medical treatment as well as the psychosocial aspects of SCD.
- The evolving understanding of the disease pathology has led to new molecular targets including adhesion molecules (e.g. P-selectin), oxidant stress and genetic approaches such as gene therapy and gene editing tools, e.g. CRISPR (clustered regularly interspaced short palindromic repeats) which has brought new hope to this old disease.

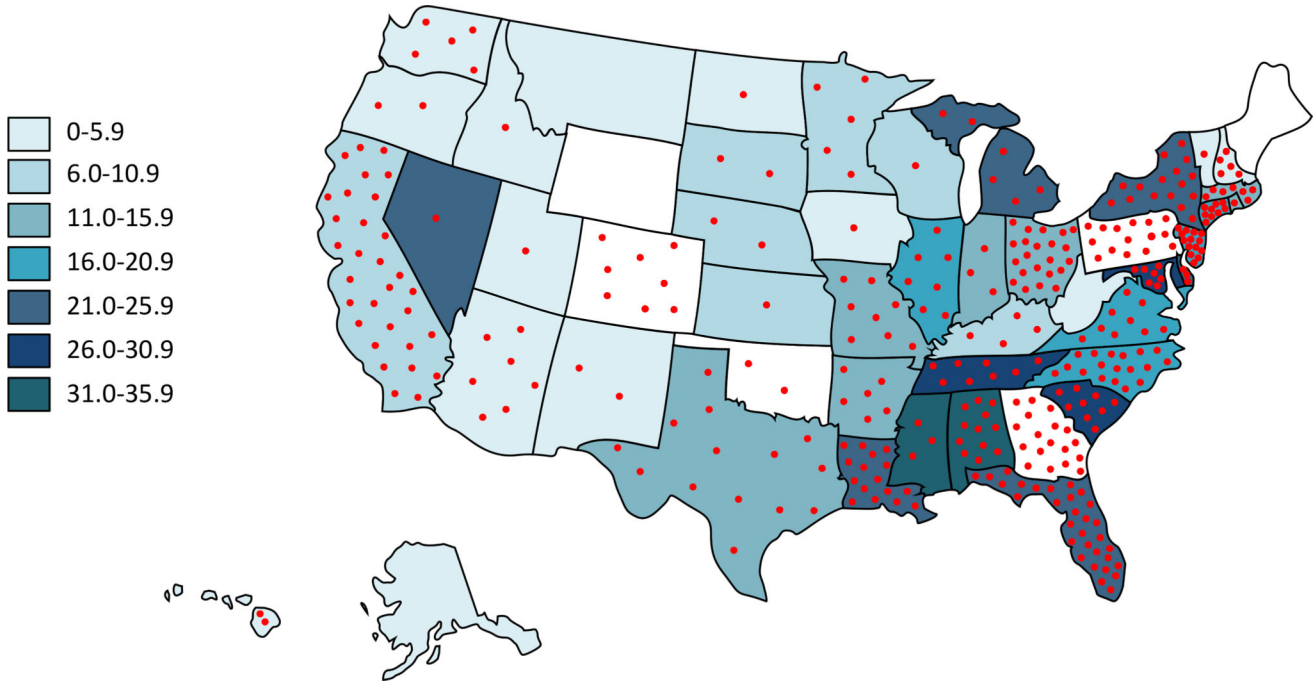
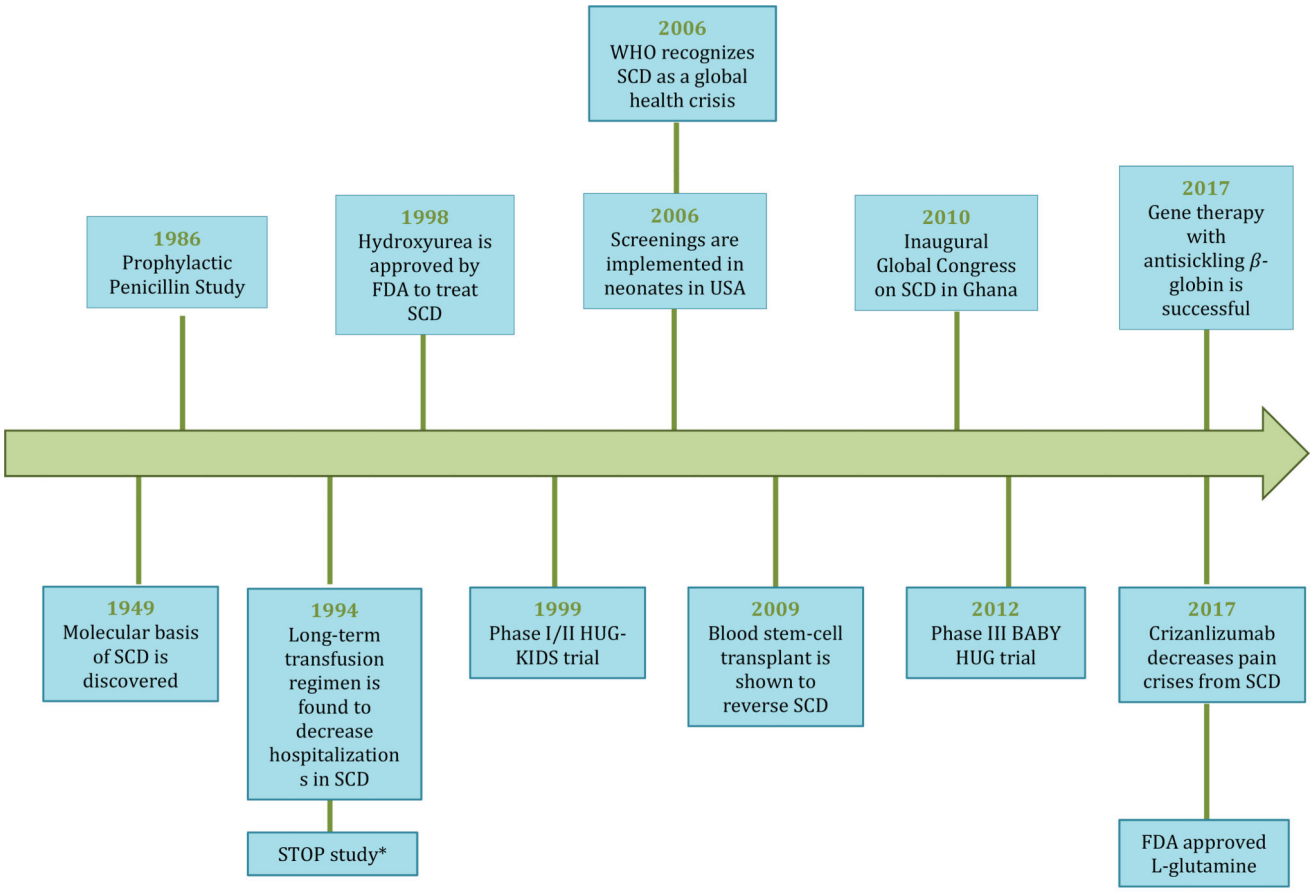


Figure 1. Number of neonates possessing sickle cell trait per state and number of SCD resources per state

The number of neonates possessing the sickle cell trait (per 1,000) neonates screened in each state, as determined by a Centers for *Disease* Control and Prevention (CDC) study [16]. Low incidence is depicted by lighter blue and high incidence by darker blue. States depicted in white were not included in the study. The red dots represent SCD resources available per state, including providers and sickle cell centers, as well as sickle cell associations, nonprofits, and foundations, according to the CDC [17]. Not depicted are six resources, which are available in Washington, DC. US map adapted from the Servier Medical Art.



*Stroke prevention in pediatric sickle cell anemia with chronic transfusion

Figure 2. Timeline of milestones in the recognition of SCD as a global crisis and treatment of the disease

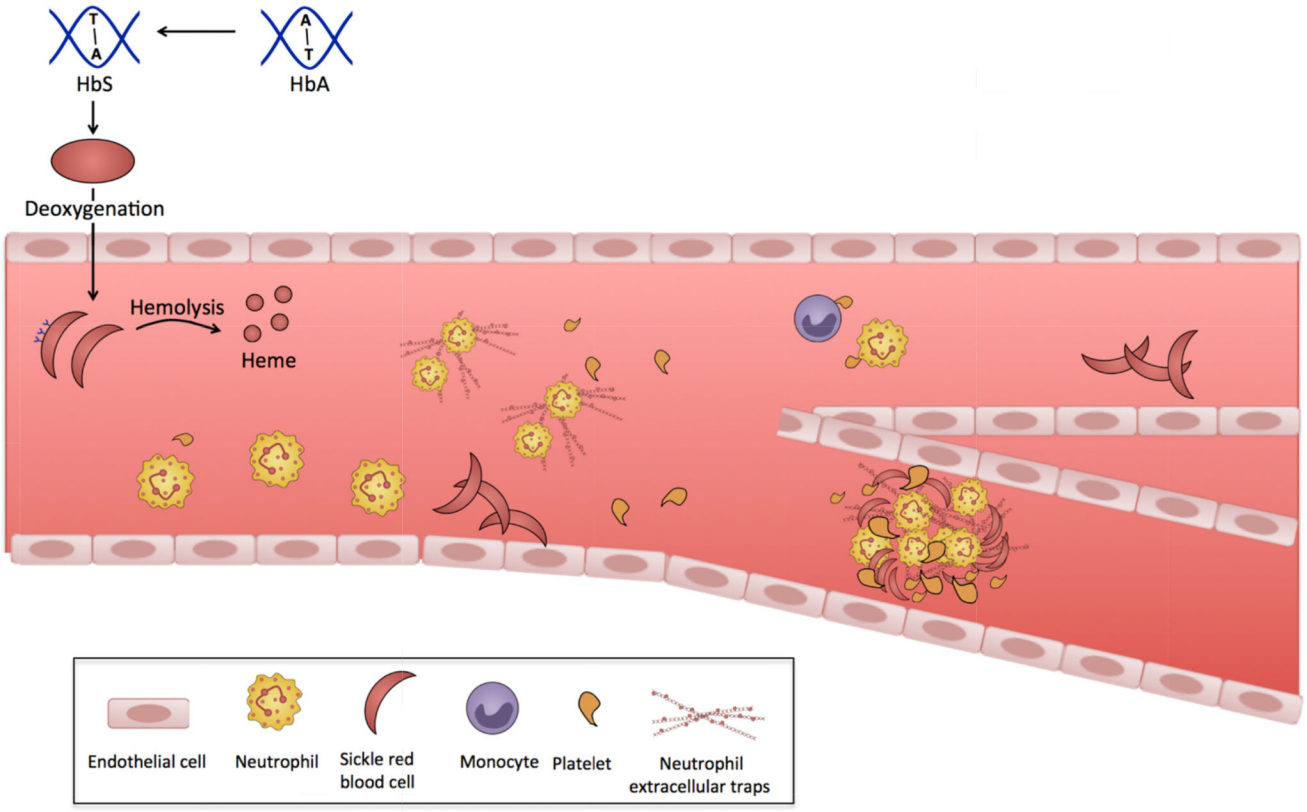


Figure 3. Neutrophil biology in SCD

When red blood cells are deoxygenated, sickle hemoglobin (HbS) polymerizes, and these cells take on a “sickle” phenotype. Hemolysis of the sRBCs produces heme microparticles activates neutrophils to release chromatin and granule proteins to form neutrophil extracellular traps. Activated platelets, found in platelet-monocyte aggregates and platelet-neutrophil aggregates, also cause neutrophils to release neutrophil extracellular traps (NETs) and capture sRBCs resulting in vaso-occlusion.

Table 1

Mitigation strategies for SCD

Sickle cell education programs
Diet and exercise counseling, SCD specific vaccination and antibiotic prophylaxis programs, addressing caregiver 'burnout', assessment of familial relationships and family caregiver roles, reproductive counseling, medication compliance, internet resources, smoking and alcohol cessation programs, education about the clinical course of SCD and adverse signs, education about benefits of personal hygiene and health, feedback mechanisms are important goals for both clinicians and SCD sufferers and their families.
Models of care
Establishment of comprehensive sickle cell disease centers, and patient/family centered medical homes (PCMH), newborn screening (NBS) programs, health educators, social workers, case managers and sickle cell nurse coordinators. Community health worker models (patient navigators, patient advocates and peer advocates).
Screening and management tools for long term complications of the disease
Screening for coronary artery disease (CAD), pulmonary hypertension (PH), and renal and cerebrovascular function (doppler echocardiography, transcranial doppler scanning, computed tomography (CT) scan and functional magnetic resonance imaging (fMRI)), activities of daily living (ADL) monitoring, and risk factor stratification. Established protocols for management of SCD specific secondary complications (avascular necrosis, proliferative retinopathy, sickle hepatopathy and priapism.
Widespread use of disease modifying agents like HU
Prescription and monitoring of HU therapy. Prospective clinical trials in adult as well as pediatric population, patient and caregiver education about the benefits of HU therapy. Development and promotion of better HU regimens.
Psychological evaluation of potentially risky population
Assessment of neurocognitive deficit, management of anxiety and depression, use of psychological coping approaches including pain coping methods and transaction models. Use of psychoeducation, cognitive behavioral therapy, and rehabilitation programs.
Reproductive health
Education about growth and reproduction, behavior and intention, including multimedia education intervention programs (CHOICES, etc.)
Health care utilization and financing programs
Financial support (insurance, copays, reimbursement, and better payment structures), increased government, industry, and philanthropic funding, nutritional therapies
Sickle cell support groups
CHAMPPS program (Choosing Health, Awareness, Mobility, Personal Power and Success), advocacy groups for SCD, ASCAA (American sickle cell anemia association)
Research and development
Prospective clinical trials with novel drugs, large-scale genome wide association studies (GWAS), use of gene therapy and gene editing technologies like CRISPR and transcription activator-like effector nucleases (TALEN).

Table 2

Evolving treatment approaches for SCD (summary of recent completed and ongoing trials)

Therapeutic agents	Mechanism of Action	Phase (Protocol #)
Anti-switching agents		
Hydroxyurea	Multiclass	FDA approved
Decitabine	HbF induction	Phase I (NCT01685515) Phase II (NCT01375608) *
Pomalidomide	HbF induction	Phase I (NCT01522547) *
HQK-1001	HbF induction	Phase I (NCT00842088) * Phase II (NCT01322269) *
AES-103	Oxy-Hb curve	Phase I (NCT01597401) * Phase II (NCT01987908) **
Senicopac	Gardos channel	Phase II (NCT00040677) * Phase III (NCT00102791) ** Phase III (NCT00294541) **
Sanguinate	Oxygen transfer	Phase I (NCT01848925) * Phase II (NCT02411708)
MP4CO	Heme-oxygenase 1	Phase I (NCT01356485) *
SCD-101	Oxy-hb curve	Phase I (NCT02380079)
GBT440	HbS polymerization inhibitor	Phase II (NCT02850406)
Anti-inflammatory and anti- neutrophil agents		
GMI – 1070	Pan-selectin inhibition	Phase I/II (NCT00911495) * Phase III (NCT02187003)
SelG1	P-selectin inhibition	Phase II ((NCT01895361) *
Sevuparin (LMWH)	P-selectin inhibition	Phase II (NCT02515838)
Regadenoson	$A_{2A}R$ agonist, iNKT inhibition	Phase II (NCT01085201)
Sulfasalazine	NF-κB inhibition	Preclinical
Statins	Upregulating eNOS levels, smooth muscle migration and proliferation	Preclinical
Propranolol	BCAM/Lu and ICAM-4(LW)	Phase I (NCT02012777)
Poloxamer 188	Multiple mechanisms and improves vascular rheology	Phase III (NCT00004408) *

Therapeutic agents	Mechanism of Action	Phase (Protocol #)
		Phase III (NCT01737814) *
IVIG	Antibody binding via the Fc- domain of the IgG molecules to the common IgG receptors. Modulate neutrophil function via FcγRIII receptors. Mac-1 stabilization.	Phase I/II trial (NCT01757418)
SC411 (Docosahexaenoic omega-3 acid)	Maintains lipid bilayer and composition of membrane phospholipids	Phase III (NCT02604368)
Anticoagulants and antiplatelet agents		
Warfarin	Vitamin K antagonism	Phase II (NCT01036802) **
Dalteparin (LMWH)	Anticoagulation via thrombin inhibition	Phase II (NCT01419977) *
Eptifibatide	Antiplatelet action via GPIIb/IIIa	Phase I/II (NCT00834899) **
Prasugrel	Reduces aggregation via ADP pathway.	Phase I (NCT01178099) * Phase II (NCT01476696) * Phase II(NCT01167023) * Phase III (NCT01794000) **
Anti-oxidants		
Inhaled NO	NO homeostasis	Phase I (NCT00023296) * Phase II (NCT00142051) ** Phase II/III (NCT00748423) *
Sildenafil	PDE5 inhibition	Phase II (NCT00492531) **
L-Arginine	NO substrate	Phase II (NCT00513617) * Phase I/II (NCT02447874) Phase II (NCT01796678) * Phase II (NCT02536170) Phase II (NCT00004412) * Phase III (NCT01142219) *
L-glutamine	NAD redox potential	Phase II (NCT00125788) * Phase II (NCT01048905) * Phase III ((NCT01179217) *#
Riociguat	Soluble guanylate cyclase stimulator	Phase II (NCT02633397)
Gene therapy		
Gamma Globin Lentivirus Vector	Gene transfer	Phase I/II (NCT02186418)

* completed

** terminated

recently approved by FDA

Table 3

Key points

- SCD is the most common congenital hemoglobinopathy; it affects almost 100,000 individuals in the US alone.
- The chronic nature of SCD has an enormous socioeconomic impact on affected communities, and SCD patients live in a state of continuous physical and psychological disability.
- In the past, management has focused mainly on primary prevention and symptomatic relief, with hydroxyurea (HU) and the recently developed L-glutamine being the only two Food and Drug Administration (FDA) approved disease-modifying drug available.
- There is a pressing need for complementary adjuvant therapies with repurposed and novel drugs as well as establishment of more comprehensive SCD centers focusing on the medical treatment as well as the psychosocial aspects of SCD.
- The evolving understanding of the disease pathology has led to new molecular targets including adhesion molecules like P-selectin, oxidant stress and genetic approaches such as gene therapy and gene editing tools, e.g. CRISPR (clustered regularly interspaced short palindromic repeats) which has brought new hope to this old disease.