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Sickle Cell Disease

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Sickle cell disease · Hydroxyurea · Transfusion · Stem cell transplantation · Gene therapy

Abstract
Background: Sickle cell disease (SCD) is among the most frequent hereditary disorders globally and its prevalence in Europe is increasing due to migration movements. ***Summary:*** The basic pathophysiological event of SCD is polymerization of deoxygenated sickle hemoglobin, resulting in hemolysis, vasoocclusion, and multiorgan damage. While the pathophysiological cascade offers numerous targets for treatment, currently only two disease-modifying drugs have been approved in Europe and transfusion remains a mainstay of both preventing and treating severe complications of SCD. Allogeneic stem cell transplantation and gene therapy offer a curative option but are restricted to few patients due to costs and limited availability of donors. ***Key Message:*** Further efforts are needed to grant patients access to approved treatments, to explore drug combinations and to establish new treatment options.

Introduction

Various congenital hemoglobinopathies are grouped under the term sickle cell disease (SCD), including homozygous SCD, HbSC disease, and HbS/β-thalassemia [1]. All these hemoglobinopathies have in common a variant of the β-globin gene (*HBB*), which leads to the exchange of the hydrophilic glutamate residue at position 6 of the β-globin chain for the hydrophobic valine. Two β-globin chains and two α-globin chains form the tetrameric hemoglobin A (HbA) of the adult, whereas the embryonic and fetal hemoglobins do not contain β-globin and are not affected by variants in *HBB*. For this reason, SCD does not manifest clinically until after neonatal age, but can nevertheless be diagnosed immediately after birth.

The product of the sickle cell *HBB* allele β^S is incorporated into the hemoglobin tetramer instead of physiological β-globin, resulting in sickle cell hemoglobin, HbS. In the deoxygenated state, HbS can polymerize through intermolecular hydrophobic interactions and impose the sickle shape on the erythrocytes. This polymerization of hemoglobin is the first event in a pathophysiological cascade that affects every organ through hemolysis, vasoocclusion, and endothelial damage and causes the systemic disease SCD.

SCD is inherited recessively. Heterozygous carriers with one β^S and one healthy *HBB* allele do not develop the disease. Homozygous SCD, on the other hand, is characterized by unpredictable crisis-like episodes of pain, chronic hemolytic anemia, loss of splenic function, and chronic damage to other organs. Patients with a compound heterozygous genotype who carry a thalassemic *HBB* allele in addition to the β^S allele produce no or almost no HbA in addition to HbS and develop a phenotype that cannot be distinguished clinically from homozygous SCD in individual cases. Patients who carry a β^C allele in addition to the β^S allele also develop the disease, but are more affected by complications of hyperviscosity rather than by hemolysis and vasoocclusion. Clinically, this is particularly evident in hearing and vision disorders caused by perfusion failures in the inner ear and retina.

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Even within the same *HBB* genotype, SCD is characterized by a remarkable inter- and intraindividual variability in disease progression and life expectancy compared to other monogenetic diseases [2]. The mechanism of disease modification that has been studied most intensively is the expression of fetal hemoglobin, HbF [3]. HbF can actively interfere with the polymerization of HbS, which is why higher HbF levels are associated with a more favorable disease course. The induction of HbF has become a target of drug and cellular therapies for SCD. In addition to genetic characteristics, SCD is also decisively influenced by environmental factors including medical treatment in particular, but also infections.

One of the infections that modify the course of SCD is malaria [4], which is often severe and fatal in young children with SCD. On the other hand, heterozygous carriers are protected against severe malaria in comparison to people who do not carry the β^S allele. In the past, this protection against severe malaria in heterozygous carriers has led to selection in favor of the β^S and similarly β^C alleles in malaria regions and thus indirectly determined the geographical distribution of the β^S trait and SCD. The migratory movements of the last centuries, decades, and years have partially broken the geographical link of SCD to malaria prevalence areas and have increasingly established SCD, originally limited to Africa, India, and the western Mediterranean region, in the Americas and Europe. This review aims to present the epidemiology, pathophysiology, complications, and treatment options of SCD and thus equip hematologists and transfusionists with the tools to treat this complex disorder.

Epidemiology

Prevalence and Incidence

It is estimated that around 312,000 children worldwide were born with SCD in 2010 [5]. Many of these children will not reach reproductive age [6, 7]. However, around 5,476,000 asymptomatic carriers were also born each year and general population growth, reduced childhood mortality with better medical care, and the continued selection advantage of heterozygous carriers in malaria-endemic areas [8] result in a continuous rise of these numbers. While newborn screening programs provide solid figures on birth prevalence, reliable estimates of prevalence in older age groups are not available due to a lack of mortality data [9].

Geographic Distribution

SCD likely originates from a founder mutation that happened 7,300 years ago [10]. Its geographical distribution has historically been determined primarily by the coevolution of the species *Homo sapiens* with *Plasmodium falciparum*. The β^S allele, like the β^C allele, is a textbook example of a balanced polymorphism. Heterozygous individuals have a selection advantage over both homozygous individuals with SCD and individuals who do not carry the β^S or β^C allele, in that they are less likely to develop a severe course of malaria [4] and at the same time experience no impairment of reproductive fitness by SCD. This situation has led to the highest prevalence of both the β^S allele and SCD in the malaria-endemic areas of sub-Saharan Africa and India. A prevalence of around 800 per 100,000 is estimated for Africa and around 200 per 100,000 for India and the Middle East [9]. However, these numbers vary greatly from region to region and are still subject to selection by malaria [8] and shaped by population movements [11].

As a result of the slave trade between West Africa and the Americas, the β^S and β^C alleles were brought to Brazil, the Caribbean, and North America from the 17th century onward. In Europe, too, SCD is predominantly a disease of immigrants and their descendants. In Central Europe in particular, the prevalence of SCD has risen sharply in recent years. Health insurance data estimate that the number of patients with SCD in Germany has increased by 50% over the past 10 years and reached around 3,200 in 2019 [12]. Despite this increase, SCD is much rarer in Germany compared to its Western European neighbors such as France, the UK, or Belgium. Due to their colonial history, the number of patients with SCD in the UK is around 5 times higher [13] and in France 10 times higher [14] than in Germany.

A national registry for patients with SCD initiated by the Society of Pediatric Oncology/Haematology (GPOH) registered a third of all patients treated in Germany [15]. Two-thirds of them come from sub-Saharan Africa, a good fifth from the Middle East. The most common genotype is homozygous SCD in 75% of patients, followed by HbSC disease in 11% of patients. Approximately 6% of patients each have HbS/β^0 or HbS/β^+-thalassemia [15].

Natural History

The course of SCD depends not only on genetic modifiers but also on environmental influences such as medical measures, exposure to infections, and climatic and social factors. The description of patients diagnosed with SCD by newborn screening in Jamaica between 1973 and 1981 and followed up until the age of 19 years comes closest to the natural course [16]. In this cohort, just over 25% of patients with homozygous SCD and 4% of patients with HbSC disease died, compared with less than 2% of healthy controls. Most of these children died in early childhood from acute chest syndrome, splenic sequestration crisis, and bacterial infections. At school age, the most common causes of death were infections with

encapsulated pathogens and strokes. The implementation of a parent education program for the early detection of splenic sequestration and the introduction of penicillin prophylaxis against pneumococcal infections resulted in a reduction of deaths already during the observation of the cohort [17, 18].

The consistent implementation of these measures in countries where newborn screening diagnoses SCD before the first symptoms appear has led to a significant reduction in mortality from SCD in childhood and adolescence in industrialized countries. Following the introduction of ultrasound screening for patients at risk of stroke and vaccination against encapsulated pathogens, particularly pneumococci, almost all patients with SCD now reach adulthood [19]. Unfortunately, this success does not continue into later life. Even under conditions of optimal medical care, the median survival of patients with homozygous SCD is around 48 years, more than 2 decades less than that of controls not affected by SCD [20].

The success in reducing the mortality rate of SCD has also been largely limited to western industrialized countries. In African countries, where most patients with SCD are born, the mortality rate for SCD is 15% in the first year of life and 36% up to the age of 5 years [6].

It would be too short-sighted to describe the course of SCD solely in terms of its influence on mortality. For the patient, recurring pain crises and the symptoms of chronic anemia dominate daily life [21]. The control group of a carefully monitored study of infants treated for SCD in the USA provides quantifiable data for the frequency of complications in SCD. Already in the 2nd and 3rd year of life, 175 hospitalizations were observed per 100 patient-years. During the 2 years of study participation, 41% of the children had four or more hospitalizations [22]. In Germany, too, slightly more than a third of patients are hospitalized at least once a year for a severe pain crisis, and one in ten suffers from at least one acute chest syndrome per year [12, 15]. The figures for pain events requiring hospitalization significantly underestimate the actual burden of disease caused by SCD, which is also determined by outpatient pain treated independently by the patient, in addition to the consequences of chronic anemia such as fatigue and lack of resilience [21]. As a result, patients with SCD have a significantly reduced quality of life [23, 24], which is on a par with that of patients with other chronic diseases such as cystic fibrosis or cancer [25].

Pathophysiology

Polymerization of HbS

The formation of hemoglobin polymers via the hydrophobic contact sites of HbS is the pathophysiological phenomenon underlying all aspects of SCD [1]. The HbS polymers impose the sickle cell shape on the erythrocytes and change their physical properties. As a result, they disrupt blood flow, particularly in small but also in large vessels, causing damage potentially to any organ. At the same time, they reduce the lifespan of the erythrocytes and lead to chronic hemolysis (Fig. 1). The different genotypes in SCD differ in detail in their pathophysiology, but they all have HbS polymer formation in common.

Only deoxygenated HbS can form polymers. Thus, both a low oxygen partial pressure and a reduced hemoglobin oxygen affinity favor the polymer formation of HbS and of sickle cells. This takes place almost exclusively in postcapillary venules harboring deoxygenated red blood cells. Tissues that retain erythrocytes at low oxygen partial pressure, for example, the red splenic pulp or the renal medulla, are particularly prone to sickle cell formation and subsequent vasoocclusion. In patients with SCD, these organs lose their functional reserve already in infancy and early childhood [26]. The oxygen affinity of hemoglobin is reduced by acidic pH values, elevated CO_2 partial pressure [27], elevated temperature, and elevated 2,3-diphosphoglycerate levels [28]. Accordingly, polymer formation of HbS is favored by hypoxia, acidosis, hypercapnia, and fever. In addition, the intraerythrocytic HbS concentration determines both the rate of nucleation and the growth of HbS polymers [29]. Even a slight increase in the intracellular HbS concentration, for example, due to exsiccosis, can trigger a vasoocclusive crisis. Conversely, the presence of α-thalassemia reduces the intraerythrocytic HbS concentration and mitigates the course of SCD [30].

The polymerization of HbS disrupts several ion channels of the erythrocyte membrane, causing the erythrocytes to lose cations and water [31]. This results in a relative dehydration of the erythrocytes, which can perpetuate a vicious circle promoting the polymerization of HbS. In addition, repeated polymerization and depolymerization of HbS can expose phosphatidylserine, which is physiologically limited to the inner layer of the lipid double membrane, on the surface of the erythrocytes. Erythrocytes with phosphatidylserine on their surface interact with other erythrocytes, leukocytes, platelets, and endothelial cells and contribute to the activation of the coagulation cascade, mediating both endothelial activation and vasoocclusion [32]. Partial loss of the membrane skeleton of sickle cells releases erythrocytic microparticles that also contribute to the activation of endothelium and coagulation [33].

Hemolysis

As a result of the mechanisms mentioned, the polymerization of HbS shortens the median lifespan of erythrocytes by 75% compared to healthy individuals to

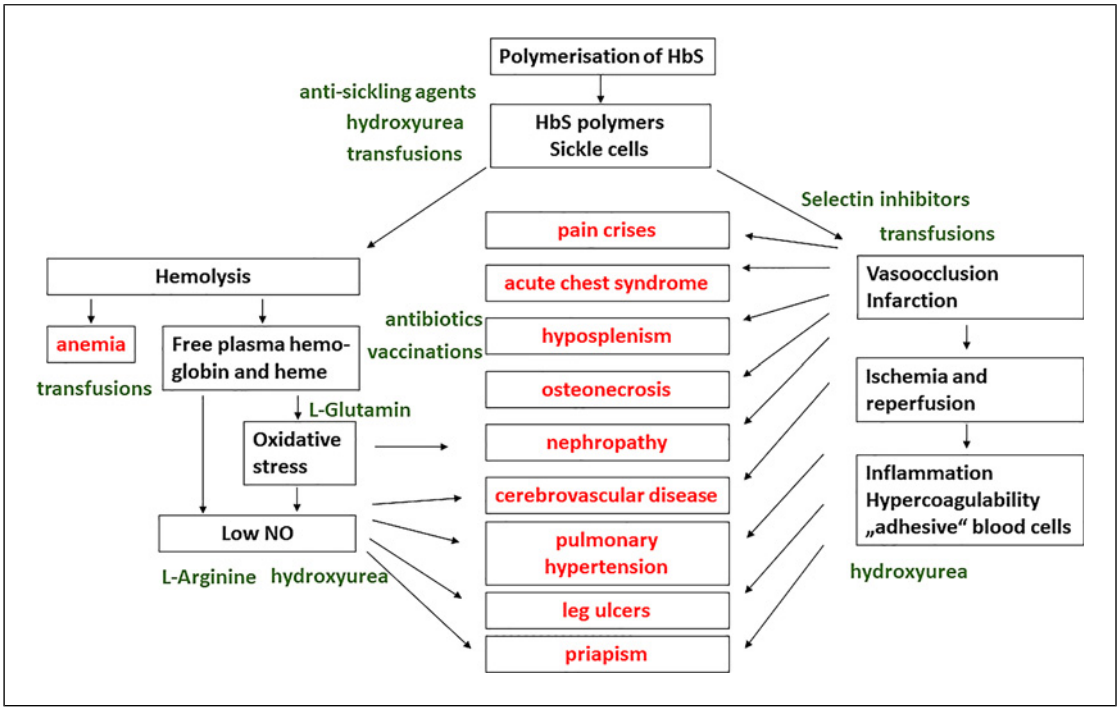

Fig. 1. Pathophysiology of SCD and treatment options. Black denotes pathophysiological processes, red clinically visible complications, and green therapeutic options. Hydroxyurea and red blood cell transfusions act at various levels of the pathophysiological cascade. The only anti-sickling agent in clinical use is voxelotor, the only selectin antagonist crizanlizumab.

approximately 30 days [34], leading to anemia. Chronic hemolysis occurs both extravascularly, especially in the spleen, and intravascularly. The relevance of intravascular hemolysis is illustrated by the fact that splenectomy in patients with SCD, in contrast to spherocytosis, does not increase hemoglobin [35]. In addition, hemolytic activity is correlated with a number of complications of SCD. These include leg ulcers, priapism, proteinuria, stroke, pulmonary hypertension, and ultimately mortality (Fig. 1) [36].

Erythrocytes in patients with SCD are exposed to oxidative stress, resulting in auto-oxidation of HbS, depletion of antioxidants such as glutathione, and damage to the cytoskeleton and cell membrane. Intravascular hemolysis releases hemoglobin and heme into the plasma where they undergo auto-oxidation and form superoxide and ultimately peroxide. At the same time, free hemoglobin in the plasma very effectively scavenges NO, antagonizes its vasodilatory effect, and activates endothelial cells and thrombocytes to express adhesion molecules [37]. The release of arginase 1 from hemolyzing erythrocytes has a similar effect, competing with NO synthase for arginine and thus reducing the bioavailability of NO [38].

Free plasma heme and hemoglobin can activate the innate immune system as a danger-associated molecular pattern. As a result, they increase the expression of adhesion molecules on blood and endothelial cells, activate neutrophils to release thrombogenic DNA, and release vasoconstrictors such as endothelin-1 [39]. Through this mechanism, hemolysis is linked to the second clinically visible pathophysiological component of SCD, vasoocclusion.

Vasoocclusion

SCD is characterized not only by immediate, painful vasoocclusive crises but also by gradual loss of organ function resulting from chronic vasoocclusion (Fig. 1). Both are caused by an interaction of erythrocytes, leukocytes, platelets, and endothelium [40]. Sickle cell erythrocytes are more rigid than normal erythrocytes and express a number of adhesion molecules that mediate interaction with endothelium, but also neutrophils and platelets. The chronic inflammation present in SCD increases the number of leukocytes and their readiness to adhere. Granulocytes interact with the endothelial cells via selectins, reducing the flow velocity in capillaries and postcapillary venules and increasing the passage time of erythrocytes in a relatively hypoxic environment. This effect partly explains why infections can trigger vasoocclusive crises. Platelets also participate in vasoocclusion through cell-cell interactions and the release of cytokines [41].

Diagnosis of SCD

Possible indicators of SCD are recurrent episodes of pain, splenomegaly, jaundice, bacterial infections, and hemolytic anemia. The origin of the affected person from a region where malaria is endemic may be indicative, but is not a *sine qua non* in view of the fact that some patients are second- or third-generation European residents. SCD cannot be detected on the basis of the blood smear alone. The detection of sickle cells is not sensitive as it depends on the preanalysis. In addition, sickle cells can also be detected in heterozygous carriers, resulting in an extremely poor specificity and positive predictive value of this test.

Diagnostic Tests

SCD is monogenically inherited and can therefore be diagnosed genetically at any age, including prenatally, by detecting the pathogenic variant in codon 6 of the *HBB* gene. The reliable detection or exclusion of mixed heterozygous HbS/β-thalassemia requires the sequence analysis of the entire *HBB* gene in addition to the analysis of codon 6.

The alternative to detecting the pathogenic variant in the *HBB* gene is the biochemical detection of the expression of HbS. This is possible from neonatal age and is carried out using protein separation methods such as high-performance liquid chromatography, capillary electrophoresis, or isoelectric focusing, alternatively also tandem mass spectrometry. None of the protein separation methods alone can reliably differentiate between HbS and other, rare hemoglobin variants. For this reason, a reliable diagnosis of SCD requires the combination of two biochemical methods [42].

Heterozygous carrier status, which is not itself associated with a disease, can also be detected both biochemically and by molecular genetics. In some healthcare systems, this is exploited to reduce the incidence of SCD through premarital screening and associated counseling [43]. Some newborn screening programs pursue the same goal by identifying at-risk couples through the detection of heterozygous newborns and referring them to counseling and preconception or prenatal diagnosis [44]. In German-speaking countries, the legislator has ruled out this procedure, as it would require the disclosure of genetic findings of minors who are unable to give consent.

Newborn Screening

In western industrialized countries, SCD meets the criteria required by the WHO for general newborn screening [45, 46]: It represents a relevant health problem [15, 47], there is an accepted, available treatment [42], and the diagnosis can be clearly established by a simple test before symptoms appear. For these reasons, SCD has been a target disease for newborn screening in many countries for decades [14, 48]. If a newborn is diagnosed with SCD, training parents to perform regular splenic palpation can reduce mortality from splenic sequestration crises [17] and daily administration of penicillin V until at least the fifth birthday can reduce the risk of fatal pneumococcal infections [49] by around 90% in each case. As a result, newborn screening has contributed significantly to reducing the mortality of infants and young children with SCD [50, 51].

In Germany, SCD has been a target disease of general newborn screening since October 2021. The test is carried out on dried blood taken between the 36th and 72nd hour of life. Different laboratories use different testing methods [52, 53]. Regardless of the method used, newborn screening for SCD is so reliable that in the event of a positive result, the newborn is presented immediately to a center experienced in SCD without requesting another dried blood sample. The center is responsible for confirming the diagnosis from an independent blood sample and informing the family about the disease and symptoms. Penicillin prophylaxis starts by the 90th day of life at the latest. For reasons of quality assurance and to collect epidemiological data, all newborns diagnosed with SCD should be recorded in the national SCD registry [15, 54]. A survey of neonatal screening laboratories revealed that during the first 17 months of neonatal screening, a total of 178 newborns with SCD were identified in Germany, corresponding to a birth prevalence of 1:5,336 or 138 newborns per year (S. Lobitz, Koblenz, personal communication).

Complications of SCD

The two basic pathophysiological mechanisms discussed above, hemolysis and vasoocclusion, correspond to the clinical symptoms of anemia and of crisis-like pain.

Anemia

The severity of chronic hemolytic anemia in SCD varies based on the *HBB* genotype and other modifying factors. Additionally, owing to the slightly reduced oxygen affinity of HbS, most patients have adapted to a lower hemoglobin level in their daily lives. Factors contributing to severe or worsening anemia may include iron or folic acid deficiency or hypersplenism.

Acute exacerbations can aggravate chronic anemia. These may result from a formation disorder, as seen in aplastic crisis triggered by a primary infection with parvovirus B19 [55–57]. The most common cause of sudden and profound anemia in young children is splenic sequestration, wherein the pooling of sickle cell

erythrocytes leads to acute splenomegaly and profound anemia. This condition is characterized by reticulocytosis and thrombocytopenia developing over a period of hours to days [17, 58]. In both aplastic crisis and splenic sequestration, a prompt blood transfusion is often lifesaving.

Vasoocclusive Pain Crisis

Most inpatient hospital admissions in SCD are for the treatment of acute pain, often referred to as a "vasoocclusive pain crisis" [22, 59, 60]. In addition to vasoocclusive pain, there are numerous other causes of pain in SCD, such as osteonecrosis, osteomyelitis, and cholecystolithiasis. Recurrent acute pain can progress to chronic pain, which affects a significant proportion of adult patients [61].

Acute pain is usually caused by vascular occlusion and often requires treatment with parenteral opioids. It is frequently the result of multifocal bone marrow infarcts. Factors such as environmental conditions (e.g., cold) or patient-related factors (e.g., fever, dehydration, overexertion, pregnancy, or sleep apnea) can precipitate sudden pain and identifying such triggers is crucial for counseling of patients [62]. Vasoocclusive pain crises exhibit an inflammatory reaction and follow a variable pattern with prodromal, initial, established, and resolving phases over several days [59, 60].

Organ-Specific Vasoocclusive Complications

Beyond the two manifestations immediately noticed by the patient, anemia and acute pain, SCD as a systemic disease affects every organ without restriction. The pathophysiology of SCD and the physiology of the organ determine how severely and at what age the respective organ is affected. For example, the slow blood flow under relatively hypoxic conditions in the red spleen pulp leads to functional asplenia in infancy, while the heart muscle, which is continuously well oxygenated, is only affected in later adulthood. Acute chest syndrome and stroke are two frequent and serious examples of organ-specific complications of SCD.

Acute Chest Syndrome

Acute chest syndrome is the second most common complication after vasoocclusive pain crises and is defined as a new infiltrate on chest X-ray with respiratory symptoms and/or fever [63]. In children, infectious causes dominate, in adults, vascular causes such as fat embolism released from the bone marrow during pain crisis are in the foreground [64, 65]. These causes all result in a pulmonary perfusion defect. Chronic damage to the pulmonary circulation leads to pulmonary hypertension in around 30% of all patients, the presence of which increases mortality up to tenfold [66–68].

Stroke

Cerebrovascular complications are among the main causes of morbidity and mortality in patients with SCD [69]. Their cumulative incidence up to the age of 30 years is estimated at 15%. Both ischemic and hemorrhagic infarctions are observed, the latter dominating especially in the third decade of life. In the remaining age groups, ischemic events occur more frequently. The reason for the infarcts is angiopathy with stenoses, aneurysms, and collateral vessel formation (Moya-Moya syndrome) [70]. In addition to acute events, silent infarcts and perfusion changes without clinically detectable symptoms also occur [71–73].

Measurement of flow velocity in intracranial arteries by Doppler sonography can identify children and adolescents at risk of ischemic infarction [74]. A regular transfusion program that permanently lowers the HbS level below 30% can prevent about 90% of strokes in these patients [75].

Phenotypic Variability and Genetic Modifiers in SCD

Next to the *HBB* genotype, the expression of fetal hemoglobin (HbF) is the modifier of SCD that is best characterized. Compound heterozygotes for HbS and alleles that mediate hereditary persistence of HbF (HPFH) do not produce HbA, but have HbF concentrations of about 20% in each erythrocyte. They do not suffer from symptoms of SCD [76, 77] and provide proof of principle that pancellular expression of 20% HbF can efficiently interfere with HbS polymerization and interrupt the pathophysiological cascade in SCD. It is important to note that the same fraction of HbF cannot cure SCD if distributed in a heterocellular pattern, which is high in some but low in other erythrocytes [78]. Besides the rare HPFH alleles, a number of modifiers of HbF expression both in *cis* and in *trans* have been shown to modulate the phenotype of SCD [3, 79]. The recognition of the beneficial impacts associated with the expression of HbF in SCD has ignited numerous efforts aimed at developing treatments, starting with hydroxyurea that has been in use for 4 decades now [80] and culminating provisionally in curative gene therapies that induce pancellular expression of HbF [81].

A second modifier of SCD that has been recognized early is the coinheritance of α-thalassemia [30]. The molecular basis of α-thalassemia are deletions that reduce the expression of α-globin. By lowering the intraerythrocytic hemoglobin concentration, α-thalassemia slows down HbS polymerization and reduces hemolysis. However, while the clinical effect is positive on some outcomes such as stroke and anemia, it is negative on others such as pain [82].

Table 1. Indications for red blood cell transfusion in SCD [42, 85, 86]

Indication	Transfusion method	Strength of recommendation	Level of evidence
Aplastic crisis	Simple	Strong	Consensus
Acute splenic sequestration	Simple (small aliquots of 3–5 mL/kg)	Strong	Consensus
Recurrent splenic sequestration	Simple (bridge to splenectomy)	Weak	Consensus
Acute hepatic sequestration	Simple (or exchange)	Strong	Consensus
Ischemic stroke	Exchange	Strong	Consensus
Primary stroke prevention	Exchange (or simple)	Strong	RCT
Secondary stroke prevention	Exchange (or simple)	Strong	RCT
Moderate acute chest syndrome	Simple	Strong	Consensus
Severe acute chest syndrome	Exchange	Strong	Consensus
Recurrent acute chest syndrome	(simple or exchange)[a]	Weak[a]	Consensus[a]
Acute multiorgan failure	Exchange	Strong	Consensus
Preoperative (>1 h general anesthesia)	Simple or exchange[b]	Weak/strong[b]	RCT
Prior to allogeneic transplant	Simple or exchange	Strong	Consensus
Complicated pregnancy	Simple or exchange	Strong	Consensus
Transfusions are generally not recommended for			
Uncomplicated vasoocclusive crisis			
Priapism			
Leg ulcers			
Avascular necrosis			

RCT, randomized controlled trials. [a]Hydroxyurea preferred. [b]Depends on extent of surgery.

HbF expression and coinheritance of α-thalassemia modify the very basic event in SCD pathophysiology. Other polymorphisms modulate events further downstream the pathophysiological cascade. A prominent example for such distal modifiers are polymorphisms in the *UGT1A1* promoter that reduce glucuronidation of bilirubin and are associated with jaundice and gallstones [82].

Management of SCD

Preventive Measures

The first measure after diagnosis of SCD is parent education regarding the risk of bacterial infection, the need for regular antibiotic prophylaxis [49], the importance of vaccinations, the clinical signs of anemia, and regular spleen palpation for early detection of splenic sequestration [42]. From the second year of age, the risk of stroke needs to be assessed by Doppler sonography until the age of 16 years [74]. Patients who are at risk receive regular red blood cell transfusion to maintain the HbS levels below 30% [42, 75].

Disease-Modifying Treatment

Disease-modifying treatment aims at ameliorating symptoms of anemia and at preventing vasoocclusive crises and long-term organ complications. Although SCD was first described more than one century ago, the development of disease-modifying drugs has been slow. Structural racism has been blamed for this situation, considering the ethnicity of a large part of affected people [83]. In Europe, only two drugs, hydroxyurea and voxelotor, are currently approved for the treatment of SCD (Fig. 1). In addition, regular red blood cell transfusions can modify the course of SCD (Table 1) [84] and currently remain the only treatment for SCD that can be applied during pregnancy without major safety concerns.

Hydroxyurea

Hydroxyurea works by increasing the expression of fetal hemoglobin, which is supposed to slow down the polymerization of HbS and prevent vasoocclusion [80]. However, in many patients with SCD, clinical improvement occurs within days of starting hydroxyurea, which is not adequately explained by the increase in fetal hemoglobin. This rapid onset of effect suggests that hydroxyurea has a positive effect on other aspects of the SCD pathophysiology in addition to increasing fetal hemoglobin. These include the release of nitric oxide with a vasodilatory effect, a reduction in neutrophil and reticulocyte counts, and a change in the surface and membrane properties of reticulocytes, leukocytes, and endothelial cells [87].

These effects translate into a reduction of vasoocclusive crises by approximately half, which was first demonstrated in adults with symptomatic SCD [88]. Subsequently, hydroxyurea was also used in infants from the age of 9 months who had been diagnosed in neonatal screening. As in adults, these unselected infants also showed a reduction in vasoocclusive

complications (acute chest syndrome, pain, dactylitis) by approximately half [22, 26]. These results led to hydroxyurea being recommended in the USA from the age of 9 months, even in asymptomatic infants with SCD [89]. In Europe, hydroxyurea is approved from the age of 2 years, but an extension of the label that allows treating infants from the age of 9 months is expected for 2024. The most important side effects of hydroxyurea include dose-dependent myelotoxicity and azoospermia.

Although the beneficial effects of hydroxyurea are well established and its use is generally recommended for patients with SCD, its use is still limited due to costs and side effects, most importantly the risk of infertility in young men. Nevertheless, the use of hydroxyurea is feasible even in low-resource countries [90, 91], reaches approximately 50% of all patients with SCD in Germany [12], and is close to 90% of those treated at university hospitals [15].

Voxelotor

Voxelotor is a hemoglobin modulator that reversibly binds as a Schiff base to the N-terminus of the α-globin chain, stabilizes the conformation of oxygenated hemoglobin, and thereby increases the oxygen affinity of HbS. This reduces the proportion of deoxygenated HbS and delays the polymerization of HbS [92].

In preclinical and clinical studies, the use of voxelotor was shown to reduce hemolysis and increase Hb levels by around 1 g/dL in a dose-dependent manner [93, 94]. As a result, voxelotor was approved for the treatment of hemolytic anemia in patients with SCD from the age of 12 years. Although the use of voxelotor counteracts the basic pathophysiological process in SCD, namely the polymerization of HbS molecules, no influence on the frequency of vasoocclusive crises has been observed to date [93].

Crizanlizumab

Crizanlizumab is a monoclonal antibody that prevents the binding of P-selectin, which is expressed on endothelium and platelets, to its ligands on the surface of leukocytes. This should reduce the adhesion of blood cells to the endothelium and improve blood flow. In the SUSTAIN study, the number of vasoocclusive crises was reduced by 45% in the crizanlizumab group compared to the placebo group [95]. Crizanlizumab was conditionally approved for the treatment of adult and adolescent patients aged 16 years and older with SCD to reduce the occurrence of vasoocclusive crises. However, the subsequent STAND trial did not reproduce the results that had led to approval and crizanlizumab was withdrawn from the European market in 2023 [96].

Regular Transfusions

The indication for regular transfusions has long been established in the primary and secondary prevention of strokes. Regular transfusions keeping the HbS percentage of total hemoglobin permanently below 30% prevents the progression of vascular stenoses [75] and reduces the risk of recurrence after a stroke has occurred [97]. Regular transfusions can also bring about an improvement in patients with recurrent acute chest syndromes and vasoocclusive crises who do not respond adequately to drug treatment [84].

An unavoidable side effect of regular transfusion therapy is siderosis. The use of partial exchange transfusions, which can be carried out either manually or as erythrocytapheresis, can minimize transfusion-related iron overload. Nevertheless, iron chelation therapy is usually necessary.

A second common consequence of regular transfusions in patients with SCD is alloimmunization [98, 99]. To prevent this, it is recommended that red blood cell concentrates are not only selected to be AB0, Rhesus, and Kell compatible, but that the Duffy, Kidd, and MNS blood groups are also taken into account [42]. This severely restricts donor selection and requires careful planning of elective transfusions.

Treatment of Complications

While the disease-modifying treatment of SCD aims to intervene in the pathophysiology of HbS polymerization, hemolysis, and vasoocclusion, the treatment of acute complications of SCD is initially aimed at alleviating symptoms and preventing secondary damage. Supportive measures such as respiratory therapy [100], physiotherapy, infusions, and O_2 supplementation contribute to this [42], but in particular, multimodal pain therapy tailored to the special features of SCD [60, 61]. The risk of infection from both encapsulated and Gram-negative pathogens that is associated with functional asplenia determines the early use of antibiotics [101]. Pharmacological interventions that interrupt the pathophysiologic cascade of SCD during the vasoocclusive crisis have been tested, but have not yet found their way into guidelines [42, 61, 85, 89] due to the lack [102] of or small [103] effect or the lack of replication in larger studies [104–109]. Erythrocyte transfusions, either "on top" or as exchange transfusion, are the only approximately causal, rapidly effective therapy for acute complications of SCD.

Transfusions

Blood transfusions in SCD serve a dual purpose: in acute anemia such as splenic sequestration or aplastic crisis, they maintain the minimum necessary hemoglobin level, stabilize the circulating blood volume, and thus prevent hemodynamic shock. In addition, the transfused erythrocytes also dilute the sickle cell erythrocytes,

improve oxygenation in the area of a vasoocclusive event, and can thus break the vicious circle of polymerization of HbS, reduced perfusion, hypoxia, and further polymerization. This interruption of the pathophysiology of SCD is aimed at vasoocclusive events such as acute chest syndrome or stroke (see Table 1 for a list of indications for red blood cell transfusion). The primary goal is not an increase in hemoglobin, but the exchange of HbS for HbA [110]. As blood viscosity and therefore the risk of vascular occlusion in SCD increase sharply when Hb values exceed 10 g/dL, an Hb value of 10 g/dL is aimed for in the event of severe complications. In order not to exceed this and still achieve an effective reduction in HbS, an exchange transfusion is used in cases of acute organ failure due to vasoocclusion, such as severe acute chest syndrome or stroke. When transfusing for splenic sequestration, it should be noted that the transfusion of healthy erythrocytes also releases the patient's own erythrocytes from the spleen and the hemoglobin level may rise unexpectedly. In order not to provoke complications of hyperviscosity, red blood cell concentrates are therefore transfused in small portions [42].

Hemolytic transfusion reactions are more frequent in SCD than in any other condition, likely due to differences between recipient and donor red blood cell antigens. It can occur up to 3 weeks after red blood cell transfusions (delayed hemolytic transfusion reaction). These reactions may be mediated by alloantibodies, but can also occur without the detection of erythrocyte-specific antibodies [111]. Hyperhemolysis, marked by the simultaneous hemolysis of both transfused and the patient's endogenous red blood cells, is a commonly observed phenomenon, often concomitant with intense vasoocclusive pain. Treatment options for hemolytic transfusion reactions include the administration of glucocorticoids, immunoglobulins, erythropoietin analogs, and complement inhibitors such as eculizumab [112]. Further erythrocyte transfusions should be withheld.

Curative Treatment

Despite all the progress made, many patients with SCD suffer from high morbidity and an immense reduction in quality of life and are therefore willing to take risks for a therapy that promises cure. Currently, hematopoietic stem cell transplantation (SCT) and gene therapy are the only curative treatment options for SCD. Unfortunately, the availability of both is restricted to high-income countries and thus to a tiny proportion of all patients with SCD.

Allogeneic SCT

Allogeneic SCT is considered the "standard of care" if an HLA-identical, healthy sibling is available as a donor [42, 113]. SCT from HLA-identical sibling donor in young children showed an overall survival rate of almost 100% and a disease-free survival rate of over 90%. These figures fall with age, reaching only 88% and 81%, respectively, for patients aged 16 years or older [114]. As HLA-identical unrelated donors are only exceptionally identified for patients with SCD [115], there are hardly any data available on the success of this transplant. Transplantation from mismatched, usually haploidentical donors is associated with a mortality rate of 10% or more [116] and is therefore reserved for a small number of patients with particularly severe disease [42, 113, 117].

In addition to the immediate complications of transplantation such as infections, GvHD, and recurrence of SCD, the long-term consequences are relevant for patients when deciding for or against a transplant. These include infertility [118] and therapy-associated neoplasia [119], in particular MDS and AML. The decision for or against SCT after an individual risk assessment is difficult to make for patients with SCD. Considering that SCD-related organ complications reduce the chances of success already during adolescence, this decision often has to be made by the patient's legal guardians and requires the advice of experienced hematologists and transplant specialists.

Gene Therapy

As a monogenic disease, SCD is particularly amenable to gene therapy, partly because a substitute for HbS is available in the form of fetal hemoglobin, HbF. Its reactivation in erythropoietic precursor cells is sufficient to cure SCD. Gene therapy benefits from the methods established in blood SCT for obtaining and manipulating hematopoietic stem cells.

Both the addition of a healthy β-globin gene and the reactivation of HbF have demonstrated efficacy in clinical trials [81, 120]. There are a number of different methods for the latter, most of which ultimately aim to inactivate the BCL11A transcription factor that suppresses HbF expression [121]. All methods used clinically to date require the collection and manipulation of autologous stem cells. The patient is then conditioned by myeloablative chemotherapy, typically with busulfan, before the manipulated blood stem cells are reinfused. The major advantage over allogeneic blood SCT is that there is no risk of graft-versus-host disease and therefore no need for immunosuppression. With the two methods of gene addition [120] and inactivation of an erythropoiesis-specific BCL11A promoter by gene editing [81] tested in larger studies, over 90% of patients achieved the endpoint of "freedom from vasocclusive crises." The median follow-up after gene therapy extends over 3 (gene addition) and 2 years (gene editing), respectively [122, 123]. Based on these results, the two gene-therapy products lovo-cel (gene addition) and exa-cel (gene editing) were approved by the FDA in December 2023 and exa-cel was

approved by the European Medicines Agency in February 2024.

Several hurdles are currently preventing the widespread use of gene therapy for SCD and will probably continue to do so for some time to come. These include the immense logistical effort and costs, as well as the side effects of myeloablative conditioning with infertility and the induction of therapy-related neoplasia. Approaches to circumvent these problems are chemotherapy-free conditioning protocols [124] and in vivo gene therapy using lipid nanoparticles targeted to erythropoietic stem cells [125].

Conclusions

SCD is a devastating multiorgan disorder. Few patients can be cured by allogeneic SCT or, most recently, gene therapy. Other patients benefit from disease-modifying treatment, mostly with hydroxyurea or with red blood cell transfusions, that needs to be continued indefinitely. Even with these treatments, acute crises and chronic organ damage limit quality of life and life expectancy. Novel treatments and rational combination of available treatments are needed to improve quality of life and extend life expectancy of affected patients.

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Conflict of Interest Statement

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Author Contributions

J.B.K. and L.T. jointly wrote the manuscript.

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