

Sickle cell disease

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Sickle cell disease is a genetic red blood cell disorder, affecting millions of people globally. This Seminar provides a comprehensive update on the disease, emphasising its complex pathophysiology involving sickle haemoglobin polymerisation, vaso-occlusion, haemolysis, and inflammation that lead to acute, life-threatening complications and progressive organ damage. We review the spectrum of the most frequent acute manifestations—vaso-occlusive crises, acute chest syndrome, stroke, and infections—alongside chronic complications affecting virtually all organ systems. Recent advances include expanded implementation of hydroxyurea in low-resource settings and the optimisation of hydroxyurea protocols, refined transfusion therapy, improved haematopoietic stem cell transplantation outcomes with alternative donor strategies, and gene therapies now approved for clinical use. Additionally, new drugs are being evaluated in clinical trials globally. We examine successful implementation strategies in low-income and middle-income countries using point-of-care diagnostics and integrated care models. Controversies and challenges include the management of sickle haemoglobin-C and haemoglobin S/β⁺ variants, cerebrovascular complication prevention, hydroxyurea use in pregnancy, and the transition from paediatric to adult care.

Introduction

The history of sickle cell disease is profoundly intertwined with the evolution of modern medicine and integrates medical discovery with cultural and geographic heritage, particularly in Africa where the disease is most prevalent.^{1,2} Since James Herrick's description of "peculiar elongated and sickle-shaped" red cells in a Black dental student from Grenada in 1910,³ sickle cell disease has served as a model for genetic, molecular, and translational research. Sickle cell disease was the first condition to be understood as a molecular disease, as described by Pauling and colleagues in 1949, and later helped to elucidate principles of gene expression, haemoglobin switching, and globin gene regulation.³⁻⁶ Yet, despite this central role in medical discovery, sickle cell disease remains under-recognised as a global health priority and is underserved in clinical care.⁷

Sickle cell disease refers to a group of inherited red blood cell (RBC) disorders caused by pathogenic variants in the *HBB* gene, resulting in the production of sickle haemoglobin S (HbS). Individuals with one copy of the mutation have sickle cell trait—a condition that confers partial protection against severe malaria—while those with pathogenic variants on both alleles (eg, sickle cell anaemia [HbSS], sickle haemoglobin-C [HbSC], and HbS-β-thalassemia) develop the clinical syndrome of sickle cell disease. The defining pathophysiological mechanism of sickle cell disease is the polymerisation of deoxygenated HbS, leading to red cell sickling, haemolysis, and vaso-occlusion accompanied by a cascade of complex pathophysiological events. This cascade drives the multisystem complications of the disease, including acute painful crisis, acute chest syndrome, stroke and cognitive impairment, and progressive organ damage.^{1,8,9}

Sickle cell disease is now recognised as one of the most common serious inherited diseases worldwide and is among the top 50 causes of non-communicable disease mortality. Global estimates suggest that more than 500 000 infants are born annually with sickle cell disease,

mostly in sub-Saharan Africa, where the mortality of children younger than age 5 years can exceed 50% in the absence of early diagnosis and treatment. The disease also remains a leading cause of death in children aged 5–14 years, and its burden is globally increasing compared with global trends for most common causes of death.^{7,10}

The global distribution of sickle cell disease reflects patterns of historic malaria endemicity and is particularly high in west and central Africa, the Middle East, India, and parts of the Mediterranean.¹¹ Population movements have led to increasing prevalence in Europe and the Americas.¹² Cultural understandings of the disease are diverse, as reflected in local names used in west Africa, such as "chwechwechwe", "nuidudui", or "akokufalobi"—the first two words referring to the sound of joint pain and the third meaning "he will die

Lancet 2026; 407: 1095–111

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Search strategy and selection criteria

We performed a careful search of the scientific literature in English from Jan 1, 2017 to May 31, 2025 using the terms "sickle cell", "hydroxyurea or hydroxycarbamide", "red blood cell transfusion", "transcranial Doppler", and "alloimmunization", "cardiac", "heart", "kidney", "vasculopathy", "SC disease", "SBetathalassemia", and "Transition". We reviewed major guidelines, including the 2014 National Heart, Lung, and Blood Institute evidence-based guidelines, the 2020 American Society of Hematology guidelines, the 2018 Sickle Cell Society's Standards for Clinical Care of Adults with sickle cell disease, the 2018 British Society for Haematology (BSH) guideline on hydroxycarbamide use in children and adults, and the 2021 BSH guideline on managing sickle cell disease in pregnancy. We also used the terms "low- and middle-income countries", "LMIC", "Africa", "India", "resource limited", "models of care", "transfusion", "newborn screening", and "point-of-care testing". We searched ClinicalTrials.gov for all ongoing trials identified as "sickle cell" or "open or recruiting".

	HbA (%)	HbS (%)	HbC (%)	HbF (%)	HbA ₂ (%)	MCV	Clinical course
Normal	95–98	0	0	<1	<3.5
Trait conditions							
HbS trait HbAS	55–65	30–40	0	<1	<3.5	Normal	Benign
HbC trait HbAC	55–65	0	30–40	<1	<3.5	Normal	Benign
β-thalassaemia trait	90–95	0	0	1–3	>3.5	Low	Benign
Disease conditions							
Sickle cell anaemia HbSS	0	80–95	0	5–15	<3.5	Normal	Severe
Sickle HbC disease	0	50–55	30–40	<3	<3.5	Normal	Moderate
HbS-β ⁰ -thalassaemia	0	80–90	0	5–15	>3.5	Low	Severe
HbS-β ⁺ -thalassaemia*	10–25	70–80	0	<3	>3.5	Low	Variable
HbS and other haemoglobin variant	0	50–60	0	Variable	<3.5	Normal	Variable

Trait conditions refer to β-globin heterozygous states, while disease conditions refer to compound heterozygous or homozygous states. Concomitant α-thalassaemia can coexist with all these conditions and affects the ratio of HbA to HbS or HbC, as shown by the range of values for each haemoglobin listing. Sickle cell genotypes are shown with the typical haemoglobins present on electrophoresis, and clinical course. The sickle or other disease conditions typically have 50–60% HbS with 20–45% of a variant haemoglobin, such as HbD, HbE, or HbOArab. Combined heterozygosity with thalassaemia also features microcytosis with low MCV. HbSS and HbSC with coinheritance of α-thalassaemia trait features a low MCV and should prompt testing for α-globin deletion. HbA=haemoglobin A. HbA₂=HbA α₂δ, subunit. HbAC=HbA-haemoglobin C trait. HbAS=HbA-sickle trait. HbC=haemoglobin C. HbD=haemoglobin D. HbE=haemoglobin E. HbOArab=haemoglobin O Arab, prevalent in Arab populations. HbS=haemoglobin S. HbSS=sickle cell anaemia. MCV=mean corpuscular volume. *S-β⁺-thalassaemia in the USA, Caribbean, UK, and northern Europe typically has 10–25% HbA, but moderate and severe forms of HbS-β⁺-thalassaemia have been identified in Europe, with a clinical phenotype similar to HbSS and HbSC.^{35,36}

Table 1: Common forms of sickle cell disease and related haemoglobinopathies by genotypes

tomorrow”. These terms reflect the visibility, pain, stigma, and fatalism historically associated with sickle cell disease in many communities.^{7,8,13}

Although major improvements in paediatric outcomes have been achieved in high-income countries (HICs) with universal newborn screening, penicillin prophylaxis, pneumococcal vaccination, treatment with hydroxyurea, and stroke prevention programmes,^{14–19} adult life expectancy remains substantially shortened.^{20,21} In low-resource and middle-resource settings, access to these interventions remains limited or absent.⁷ Historical neglect, structural inequities, and a legacy of racial and geographical marginalisation have contributed to underinvestment in research, clinical infrastructure, and pharmaceutical innovation for sickle cell disease—although this trend is beginning to shift globally.^{22,23} Recent years have seen a growing pipeline of disease-modifying therapies, including crizanlizumab, voxelotor, and L-glutamine, alongside curative options, such as haematopoietic stem cell transplantation (HSCT) and transformative gene therapy.^{24–29} However, access remains geographically disparate with high-prevalence countries having the fewest clinical trial sites and scarce or no commercial availability of approved treatments. Withdrawal of new drugs and new treatments from the market^{30,31} have had a global impact, even in high-resource setting.

Despite great clinical need, progress in care delivery and health system response remain slow. WHO has issued resolutions on sickle cell disease, and several international campaigns have recently been launched, but most affected individuals still lack access to timely diagnosis and essential treatments. This fragmented response has led to major discrepancies in survival, with HICs seeing 80–90% survival into adulthood, but with a peak mortality in late adolescence, while in low-income regions, most children with sickle cell disease die without ever being diagnosed.⁷

This Seminar is not an exhaustive summary of the pathophysiology, management, or treatment of sickle cell disease, for which readers are referred to recent guidelines. This Seminar provides an updated synopsis of sickle cell disease with a global perspective on its pathophysiology, clinical manifestations, therapeutic landscape, and public health implications. Persistent gaps in access and outcomes, emerging therapeutic and diagnostic innovations, and the urgent need for integrated strategies that align scientific progress with global equity are highlighted here. In doing so, we aim to reframe sickle cell disease not only as a medical condition, but as a barometer of the capacity—and willingness—of global health systems to deliver on the promise of modern medicine for all.

Epidemiology and the global burden of disease

The global epidemiology of sickle cell disease is evolving due to demographic shifts, improved survival, and population movement.⁷ While national incidence rates remained relatively stable from 2000 to 2021, the absolute number of births with sickle cell disease increased by nearly 14%, reaching an estimated 515 000 annually, primarily driven by population growth in sub-Saharan Africa and parts of Asia. The number of individuals living with sickle cell disease increased by more than 40% during the same period, surpassing 7.7 million globally.¹⁰ This expansion reflects both higher birth prevalence and improved childhood survival, particularly in HICs, contributing to the emergence of a growing adult population with sickle cell disease and evolving clinical complexity. Nevertheless, sickle cell disease remains a major contributor to mortality in those younger than age 5 years in low-income regions where access to newborn screening, disease-modifying therapies, and essential care is limited.⁷ At the same time, increased global population movement has reshaped the epidemiology of sickle cell disease in high-income regions, including Europe, where the disease is still classified as rare but has rising prevalence.³² Despite the growing number of patients in HICs in the EU and North America, reliable epidemiological data remain scarce due to fragmented registries, inconsistent use of diagnostic coding, and limited harmonisation across health systems.^{32,33} A recent systematic review confirmed substantial gaps in birth prevalence and genotype-specific data, particularly in regions with high expected

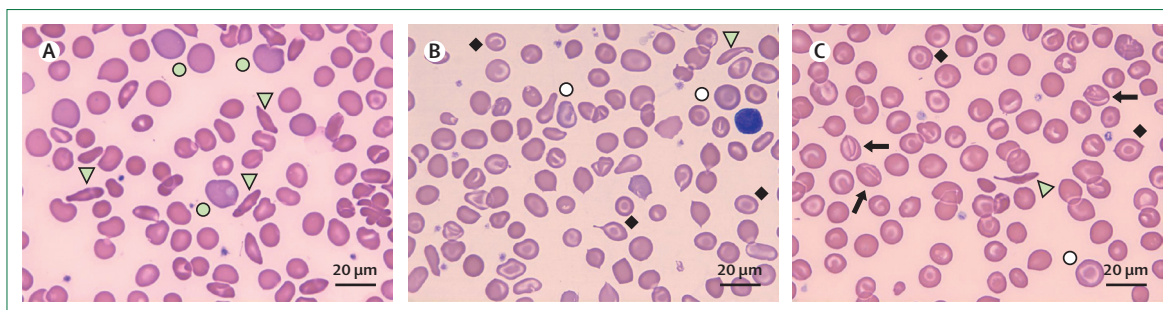


Figure 1: Peripheral blood smear morphology in patients with sickle cell disease of different genotypes

(A) Homozygous HbSS: numerous sickled erythrocytes (triangle) and reticulocytes (green circle). (B) Compound heterozygous HbS- β^0 -thalassaemia: sickle cells (triangle), numerous target cells (diamond), and target reticulocytes (white circle). (C) Compound heterozygous HbSC: similar feature to panel B, with the addition of characteristic cells with mild sickling (arrow) typical of this genotype. Images were taken with LEICA DM2000 LED optical microscope, DMC4500 Camera, and $\times 100$ oil lenses. HbS=haemoglobin S. HbSC=sickle haemoglobin-C. HbSS=sickle cell anaemia.

burden.³⁴ These data limitations hinder the development of adequate health policies, guidelines, resource allocation, and care models. Addressing these challenges will require sustained global investment in harmonised surveillance, cross-border collaboration, and equitable access to prevention and treatment strategies.^{7,21–23,32}

Diagnosis

Sickle cell disease results from the inheritance of abnormal β -globin alleles carrying the sickle mutation in the *HBB* gene (Glu6Val; β^S). The most common and usually most severe form of sickle cell disease is homozygous HbSS, where both parents pass on the β^S allele that allows the formation of the pathological haemoglobin tetramer ($\alpha_2\beta_2^S$; HbS). Other clinically relevant genotypes include compound heterozygous states, such as HbS- β^0 -thalassaemia (also known as sickle cell anaemia), HbSC, HbS- β^+ -thalassaemia, and combinations of HbS with rare variants, including HbSD (double heterozygous) or HbSOArab (haemoglobin O, prevalent in Arab populations). All these genotypes produce sufficient HbS to cause sickling (table 1 and figure 1).^{35,36} In contrast, HbAS (haemoglobin A, sickle cell trait) is not a form of sickle cell disease, although evidence shows an association with specific health risks.³⁷

Diagnosis of sickle cell disease is straightforward due to the abundance of haemoglobin in blood. HbS and other variants can be reliably detected by electrophoresis, isoelectric focusing, capillary electrophoresis, or high-performance liquid chromatography. Solubility and chemical tests are less reliable and should not be used alone. DNA-based techniques and mass spectrometry are promising in large scale screening programmes, although they have not altered diagnostic approaches to date.³⁸ Point-of-care testing is increasingly being used both for population screening and newborn screening, especially in low-income and middle-income countries (LMICs).^{39,40}

Early diagnosis from newborn screening is a cornerstone of modern sickle cell disease management and universal newborn screening is recommended.^{7,41–43} Universal newborn screening enables timely

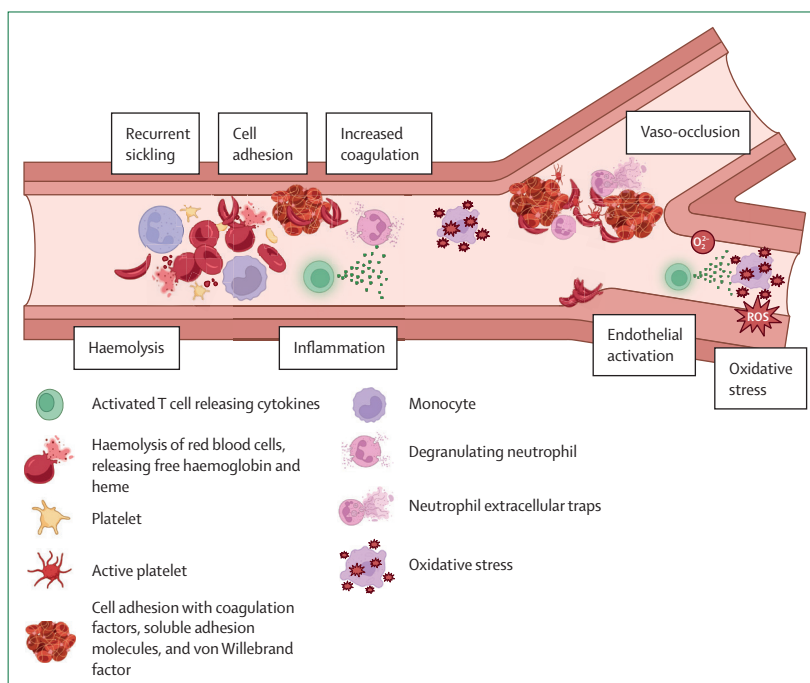


Figure 2: Cyclic pathophysiology of sickle cell disease and main cellular interactions and processes that lead to vaso-occlusion and tissue injury

Erythrocytes undergo hypoxia-induced sickling due to intracellular HbS polymerisation with resultant blood hyperviscosity and stasis, damage to endothelium, transient micro-vascular ischaemia, and subsequent intimal hyperplasia. Moreover, other circulating blood cells and plasma factors (eg, von Willebrand factor and ADAMTS13, coagulation factors, soluble adhesion molecules, inflammatory molecules, and products of haemolysis) have abnormal interactions with the endothelium. This multistep and multifactorial process leads to short-term tissue hypoxia, long-term inflammation, and endothelial vasculopathy.^{12,44–47} HbS=haemoglobin S. ROS=reactive oxygen species.

implementation of life-saving interventions that considerably reduce morbidity and mortality in early childhood. Prompt diagnosis allows for the initiation of penicillin prophylaxis and pneumococcal vaccination to prevent life-threatening infections. Newborn screening also facilitates early parental education to recognise crucial signs, such as fever, splenic sequestration, and stroke. Additional benefits include folic acid supplementation, transcranial Doppler screening to assess

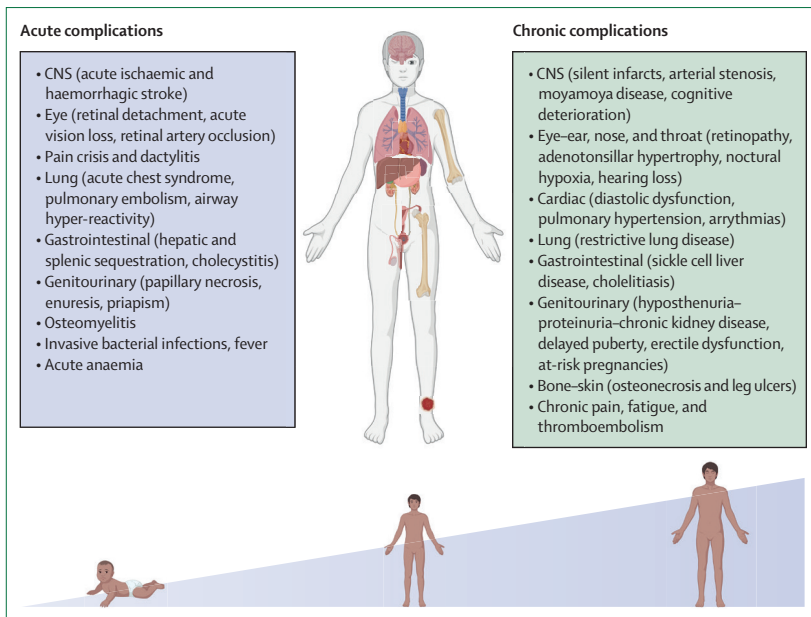


Figure 3: Acute and chronic complications, increasing with age. The list is not exhaustive.

	Clinical manifestations	Pathophysiology	Treatment
Acute painful crisis	Dactylitis; pain in the sternum, ribs, or vertebrae; pain in the long bones; priapism	Vaso-occlusion with hypoxia-reperfusion injury, inflammation, increased red blood cell adhesion, and nervous system sensitisation (central and peripheral)	Hydration; analgesia
Infection-fever	Bacteraemia or sepsis; meningitis; osteomyelitis; pneumonia; malaria	Splenic dysfunction; inflammation; necrotic bone	Antibiotics; surgery
Acute anaemia	Splenic sequestration; transient aplastic crisis; transfusion reaction; papillary necrosis in the kidney	Erythrocyte sickling; infection; sequestration; hyperhaemolysis	Red blood cell transfusion; management of hyperhaemolysis
Acute chest syndrome	Chest pain; dyspnoea	Ischaemia; infection; infarction	Antibiotics; transfusion; incentive spirometry; oxygen
Stroke	Haemorrhagic or ischaemic	Ischaemia; infarction; haemorrhage	Red blood cell transfusion

This list is not exhaustive.

Table 2: Most frequent clinical acute complications in sickle cell disease

stroke risk, and access to genetic counselling, which empowers families to make informed reproductive choices. Collectively, these interventions have transformed sickle cell disease from a frequently fatal paediatric condition into a chronic disease with improved outcomes when identified early.

Pathophysiology

The pathophysiological mechanisms of sickle cell disease start from the inheritance of the mutation leading to the production of HbS, which polymerises when deoxygenated. These intraerythrocytic HbS

polymers distort the shape of the RBCs leading to characteristic crescent moon or sickling morphology. These sickled RBCs occlude blood vessels causing ischaemic tissue damage and cyclical ischaemia or reperfusion. Sickled RBCs undergo premature haemolysis, releasing toxic erythrocyte contents into the plasma, such as free haemoglobin and arginase that in turn deplete nitric oxide bioavailability, thus triggering vasoconstriction.¹⁻³ The downstream consequences of HbS polymerisation are not fully understood, but include abnormalities across biological processes, including inflammation, oxidative stress, blood coagulability, vascular endothelial function, nitric oxide metabolism, expression of adhesion molecules, and immune function (figure 2).⁴⁴⁻⁴⁷

Additionally, sickle cell disease leads to progressive multiorgan damage during the lifespan, which includes hyposplenism, renal impairment, cerebrovascular disease, avascular necrosis of bones and joints, cardiopulmonary complications, retinopathy, hepatopathy, and priapism. These underlying pathophysiological processes remain active throughout life, silently causing cumulative organ damage with time. Consequently, patients have a reduced quality of life and have variable clinical manifestations that evolve with aging.⁴⁸

Clinical manifestations, monitoring, and management

Clinical manifestations of sickle cell disease start in infancy and can present as acute and life-threatening emergencies or as progressive organ damage (figure 3).

Acute complications

A wide spectrum of acute complications (table 2) characterise sickle cell disease, reflecting the intricate pathophysiology of intravascular sickling, endothelial dysfunction, inflammation, ischaemia-reperfusion injury, and immune compromise. Despite advances in comprehensive care in high-resource settings, acute events remain unpredictable, have variable frequency and severity between patients, and continue to cause considerable morbidity and mortality.^{1,2,49,50} Acute complications drive health resource use and deleteriously affect patient quality of life, socioeconomic opportunities, and survival.^{21,51}

Acute vaso-occlusive episodes are the most common clinical manifestation of sickle cell disease and result primarily from microvascular occlusion and tissue ischaemia. Acute vaso-occlusive episodes are subdivided into the following categories: acute uncomplicated pain crisis or painful vaso-occlusive crises, acute chest syndrome, splenic or hepatic sequestration, and priapism.

Acute uncomplicated pain crisis or painful vaso-occlusive crisis is defined as an acute episode of pain with no other attributable cause aside from sickle cell disease. In infants, vaso-occlusive crisis often manifests as dactylitis—the earliest clinical sign—while in older children, adolescents, and adults, pain typically affects

the extremities, back, and chest. Vaso-occlusive crises are the leading cause of emergency visits and hospital admissions across all age groups, with frequency and severity increasing with age. Rates of hospitalisation for acute pain are also associated with increased mortality.^{52,53} Vaso-occlusive crisis results from complex interactions between sickled erythrocytes, endothelial cells, leukocytes, and platelets, leading to microvascular occlusion, tissue ischaemia, and hypoxia-reperfusion injury. This cascade is amplified by inflammation, increased RBC adhesion, and both central and peripheral nervous system sensitisation. Nociceptor hypersensitivity to mechanical, heat, and cold stimuli, exacerbated by recurrent hypoxia or reoxygenation, contributes to pain persistence. Management follows established protocols emphasising rapid analgesia—typically non-steroidal anti-inflammatory drugs and opioids titrated to pain severity—yet emerging research implicates mast cell activation, peripheral hyperalgesia, and altered pain pathways, underscoring the need for new targeted analgesic strategies. Recent guidelines advocate for a more comprehensive conceptual framework that distinguishes acute pain episodes from chronic sickle cell disease pain and recognises so called acute-on-chronic pain states, which might require distinct therapeutic approaches.^{54–56}

Acute chest syndrome is characterised by the presence of a new pulmonary infiltrate plus symptoms, such as fever, chest pain, tachypnoea, cough, wheeze, and acute hypoxia. Acute chest syndrome is a major cause of hospitalisation and mortality, particularly in adolescents and adults. The aetiology is multifactorial, often involving infection, fat embolism, or rib infarction. Management includes early administration of broad-spectrum antibiotics targeting *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*, with supplemental oxygen, positive pressure, and transfusion therapy as needed. In cases of progressive respiratory decline or hypoxaemia, urgent exchange RBC transfusion is indicated with prompt and well-structured organisation to deliver emergent and specialised care.^{57,58}

Splenic sequestration crisis is defined based on patient presentation with acute left upper quadrant pain, the presence of an enlarged spleen, and an acute decrease in haemoglobin concentration of at least 2 g/dL greater than baseline. Although splenic sequestration crisis is historically more frequent in those younger than age 5 years, it is now associated with onset later in life due to the widespread use of hydroxyurea in infancy.^{59,60} Splenic sequestration crisis can be under-recognised in non-SS genotypes, particularly in older individuals. Hepatic sequestration crisis is defined based on manifestations of acute right upper quadrant pain, hepatomegaly, and an acute decrease in haemoglobin concentration of around 2 g/dL compared with baseline.

Priapism is the presence of a sustained, unwanted erection due to obstruction of penile venous outflow by

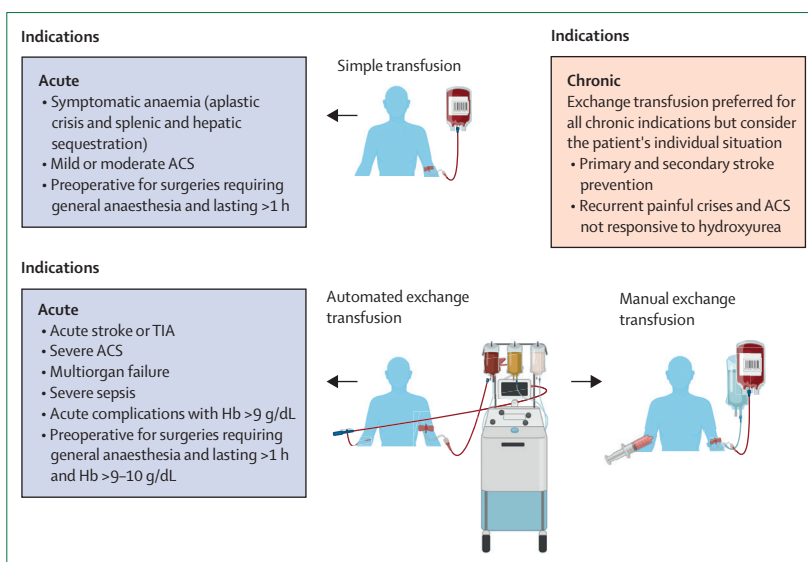


Figure 4: Simple versus exchange transfusion for acute and chronic complications of sickle cell disease. In settings where automated exchange transfusion is not possible, manual exchange transfusion can be performed.^{61–65} ACS=acute chest syndrome. Hb=haemoglobin. TIA=transient ischaemic attack.

sickled RBCs. Medical intervention for priapic episodes lasting beyond 4 hours is essential as prolonged episodes can lead to impotence.

Invasive bacterial infections remain a leading cause of mortality in young children with sickle cell disease, owing to functional asplenia that typically develops within the first few years of life. Loss of splenic function increases susceptibility to encapsulated organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* type b.⁶¹ The widespread use of pneumococcal conjugate vaccines has considerably reduced the incidence of invasive pneumococcal disease, although emerging non-vaccine serotypes and limited vaccine access in low-income settings remain concerns, prompting a shift in attention to other causes of invasive bacterial infections, such as *Salmonella*, and the need for effective broader vaccines. Penicillin prophylaxis from birth to age 5 years, parental education, and prompt medical evaluation with empirical antibiotic administration for febrile episodes are essential pillars of care.⁶²

Acute anaemia can result from splenic sequestration, transient aplastic crisis typically due to parvovirus B19, or accelerated haemolysis, including delayed haemolytic transfusion reactions. Transfusion support is often required, but care should be taken to avoid overcorrection and hyperviscosity. Target haemoglobin and use of simple versus exchange transfusion (manual or automated) should be individualised.^{63–66} Indications for transfusion are summarised in figure 4.

Stroke is among the most devastating complications of sickle cell disease as it can lead to neurocognitive deficits, physical deficits, or both. Stroke is typically ischaemic in children and haemorrhagic in adults. Before the implementation of annual transcranial Doppler

screening in children aged 2–16 years, stroke affected up to 10% of children with HbSS. Acute stroke presentation includes the sudden onset of neurological deficits, which should be presumed to indicate cerebrovascular injury until proven otherwise. Brain MRI and magnetic resonance angiogram—with diffusion-weighted, perfusion, and angiographic sequences—are preferred, although CT remains acceptable when MRI is not immediately available. Acute ischaemic stroke requires emergent exchange transfusion, followed by chronic transfusion therapy to prevent recurrence.^{1,2,48,67}

Cholecystitis in patients with sickle cell disease presents similarly to the general population with right upper quadrant pain, nausea, vomiting, fever, and jaundice. Gallstones are pigment stones from chronic haemolytic anaemia. Symptomatic stones are managed with elective cholecystectomy.^{1,2,41}

Osteomyelitis occurs more frequently in children with sickle cell disease and can mimic an uncomplicated pain crisis with intense pain usually in the extremity. Patients are often febrile and have persistent focal pain despite administration of analgesics. Imaging is not always definitive but is preferably performed with MRI when available. *S aureus* remains the most common cause of osteomyelitis in sickle cell disease, but *Salmonella* is disproportionately represented compared with patients with non-sickle cell disease. Treatment requires

parenteral antibiotic therapy, analgesia, and, rarely, debridement in advanced cases.^{1,2,41}

Retinal detachment is an ophthalmological emergency, presenting with sudden visual changes, such as flashes, floaters, and curtain-like shadows. Retinal detachment results from repeated sickling in the retinal microvasculature, causing ischaemia, neovascularisation, fibrovascular proliferation, and vitreoretinal traction. Prompt surgical intervention is required to maximise the chance of preserving vision.⁴¹

Despite improvements in early diagnosis and supportive care, these acute complications are life-altering and in some cases life-threatening and disproportionately affect individuals with restricted access to specialised care. Strategies to prevent and manage these events should be integrated into broader health system responses to reduce preventable morbidity and mortality in sickle cell disease.⁷

Chronic complications

Compared with acute sickling events, the pathogenesis of chronic organ damage in sickle cell disease is less well understood but is a major driver of reduced quality of life, morbidity, and premature mortality. Organ dysfunction results from the cumulative effects of vaso-occlusion, chronic haemolytic anaemia, repeated ischaemia-reperfusion injury, and endothelial

	Key manifestations	Screening and monitoring	Specialist to involve	Treatment
Kidney	Hyposthenuria; glomerular hyperfiltration; albuminuria; chronic kidney disease	Annual renal function; microalbuminuria; proteinuria	Nephrologist	ACE inhibitors, angiotensin receptor blockers, hydroxyurea
Eye	Retinopathy	Retinal exam from age 10 years	Ophthalmologist	Laser photocoagulation or vitreo-retinal surgery according to stage and complication
Heart	Diastolic dysfunction; arrhythmias; cardiomyopathy	Electrocardiogram; echocardiogram; electrocardiogram Holter	Cardiologist	According to clinical manifestation
Lung	Restrictive lung disease; pulmonary hypertension	Echocardiogram with tricuspid valve regurgitation measurement and N-terminal pro-B-type natriuretic peptide if symptomatic	Pulmonologist or pulmonary hypertension specialist	Disease modifying therapy (eg, hydroxyurea or RBC transfusion); vasodilator therapy for selected patients; anticoagulation if no moyamoya disease
Liver	Jaundice; gallstones	Abdominal ultrasound	Gastroenterologist or general surgeon	Cholecystectomy
Bone and joints	Osteonecrosis	Assess chronic intermitting pain; x-ray imaging followed by MRI if present	Orthopaedics or physical therapist	Physical therapy; waking aid; core decompression; joint replacement
Skin	Clinical exam	Wound exam	Dermatologist, plastic or general surgeon, or wound-care specialist	Local treatment; antibiotics and painkillers when need
Brain	Ischaemic and haemorrhagic stroke; silent infarcts; cognitive decline	Transcranial Doppler in children; MRI at least once when older than age 6 years and then in adults*; cognitive assessment	Neurologist or neuropsychologist	Hydroxyurea, RBC transfusion
Chronic pain or psychosocial	Chronic pain or mental health	Assess regularly	Pain specialist or psychologist	According to multidisciplinary team evaluation

This list is not exhaustive.^{7,41,56,67-69} ACE=angiotensin-converting enzyme. RBC=red blood cell. *Surveillance protocols differ according to setting.

Table 3: Main chronic organ complications with suggested monitoring and multidisciplinary management

dysfunction. Although they are harder to quantify, repeated acute events requiring interface with the health-care system increases the likelihood of iatrogenic complications, including drug-induced renal insults, nosocomial infection, and thromboembolic complications. Repeated blood transfusions can lead to iron overload with resultant hepatopathy, endocrinopathy, and cardiomyopathy if untreated. By age 30 years, chronic complications become the dominant clinical challenge for most individuals with sickle cell disease, considerably impairing quality of life and increasing health-care use.^{48,51}

Virtually all organ systems can be affected by sickle cell disease (table 3), but the most life-threatening complications involve the kidney, heart, and lungs. Retinopathy, osteonecrosis, chronic pain syndromes, priapism-related impotence, and silent cerebral infarcts with cognitive decline also substantially affect quality of life.

Sickle nephropathy often begins in childhood with impaired urine concentrating ability and glomerular hyperfiltration, eventually progressing to albuminuria, reduced glomerular filtration rate, and end-stage renal disease.⁷⁰ Recent data confirm that up to one-third of adults with sickle cell disease develop overt proteinuria or decreased glomerular filtration rate, and kidney dysfunction is independently associated with early mortality. Hydroxyurea and angiotensin-converting enzyme inhibitors remain first-line therapies for reducing albuminuria and slowing progression. Enuresis is another frequent complication that affects quality of life. Genetic modifiers, such as high fetal haemoglobin (HbF) levels and α -thalassaemia trait have a protective effect on nephropathy, possibly by reduced haemolysis and endothelial stress.⁷⁰⁻⁷²

Retinopathy is commonly begins during adolescence, particularly in those with HbSC. Recent evidence suggests that not only haemodynamic factors but also blood viscosity and red cell deformability play a major role in the pathogenesis of retinopathy.⁷³⁻⁷⁵ A 2025 study showed that individuals with higher HbF levels have significantly lower prevalence of proliferative sickle retinopathy, supporting HbF as a key preventive target.⁷⁶

Optical coherence tomography angiography and ultra-widefield imaging now enable earlier detection of retinal microvascular changes, even in children. These technologies could allow targeted early intervention before visual impairment occurs.⁷⁷

Cardiac dysfunction—particularly diastolic dysfunction, myocardial fibrosis, arrhythmias, and pulmonary hypertension—has emerged as a major contributor to mortality in patients with sickle cell disease. While high-output cardiomyopathy from chronic anaemia was long considered important, newer imaging and biomarker studies reveal that diffuse myocardial fibrosis develops early, often silently, and contributes to both systolic and diastolic dysfunction. Cardiovascular MRI has revealed

elevated extracellular volume fraction even in asymptomatic adolescents, correlating with reduced functional capacity and early left atrial stiffening.⁷⁸

Cardiac arrhythmias, particularly atrial fibrillation and supraventricular tachycardias, are increasingly recognised in adults with sickle cell disease and are associated with myocardial scarring, chamber dilation, and autonomic dysfunction. Hospitalisations for arrhythmia are rising in sickle cell disease cohorts, and these events often coincide with acute chest syndrome or high-output states. Continuous electrocardiogram monitoring or Holter assessments could be warranted in patients at high risk, especially those with diastolic dysfunction or myocardial fibrosis.⁷⁸⁻⁸¹

Echocardiographic indices, particularly elevated tricuspid regurgitant velocity and abnormal diastolic filling patterns, are strong predictors of early mortality in sickle cell disease, while echocardiography and cardiac MRI provide important prognostic insights.^{41,57,68,82,83} Pulmonary hypertension, which requires confirmation by right heart catheterisation, is also associated with increased mortality.^{41,57,82} Recent studies suggest that left atrial dysfunction and diffuse myocardial fibrosis might represent a restrictive cardiomyopathy phenotype, linking myocardial fibrosis, pulmonary pressures, and adverse outcomes.⁸³ Disease-modifying therapies, such as hydroxyurea and chronic transfusions, could mitigate the progression of myocardial fibrosis, but the benefit of pulmonary hypertension-targeted drugs (eg, bosentan or riociguat) is unproven.^{57,68} Since organ damage begins in childhood, screening for its presence followed by management with a multidisciplinary team and referral to organ specialists with experience in sickle cell disease should start in childhood.⁶⁹

Established treatments

Comprehensive care has been for many years the framework of care delivery for sickle cell disease.⁸⁴ Multidisciplinary management throughout life and service provision for day-by-day management, acute emergencies, and chronic complications require coordination between primary care, subspecialists, regional hospitals, and expert centres. Minimal requirements of care are newborn screening and early diagnosis, penicillin prophylaxis, vaccinations against encapsulated bacteria and influenza, protocols for management of fever, stroke screening with annual transcranial Doppler screening at ages 2–16 years, and the ability to offer treatment with hydroxyurea. Parent education and involvement in health management, and guidance on how to access pathways of care for acute and chronic complications are also necessary.^{41,61,66,69}

Hydroxyurea

Hydroxyurea remains the cornerstone of disease-modifying therapy for sickle cell disease, with more than three decades of clinical evidence confirming its ability to

induce fetal haemoglobin (HbF), reduce vaso-occlusive morbidity, and improve survival.^{16,85–87} Its principal mechanism—ribonucleotide reductase inhibition leading to S-phase arrest and stress erythropoiesis—promotes HbF induction, while additional HbF-independent effects include improved erythrocyte hydration and rheology, reduced leucocytosis and inflammation, and nitric oxide-mediated vasodilation.^{1,2} National guidelines provide evidence-based recommendations for initiating and monitoring the use of hydroxyurea therapy in sickle cell disease and consensus treatment protocols for its implementation. Indications for the initiation of hydroxyurea vary according to sickle cell disease genotype and among countries. Indications are typically based on the frequency and severity of vaso-occlusive crises; however, recent years have seen a harmonisation of practices, with a more widespread indication to start hydroxyurea at age 9 months for the most severe genotypes.^{41,87,88} Long-term studies have shown sustained reductions in painful crises, acute chest syndrome, transfusion needs, and mortality.^{89,90} Hydroxyurea is administered orally once daily, typically starting at 15–20 mg/kg per day, with upward titration every 8–12 weeks to achieve the maximum tolerated dose, defined by mild myelosuppression. Clinical trials have established hydroxyurea efficacy across the lifespan: in infants, the BABY HUG trial showed reduced vaso-occlusive events and acute chest syndrome even at low fixed doses;¹⁷ in children, TWITCH showed non-inferiority of hydroxyurea compared with transfusion for primary stroke prevention;⁹¹ and in adults, long-term follow-up of the original Multicenter Study of Hydroxyurea documented sustained survival benefit.⁹⁰ These data underpin contemporary strategies of early and proactive hydroxyurea initiation. Contemporary pharmacokinetics-guided and individualised escalation approaches allow attainment of higher HbF levels (>30%) with near pan-cellular distribution, which are outcomes that approach those achieved by curative therapies⁹² and point towards a pharmacokinetics-guided approach instead of a weight-based strategy for personalised therapy.

Recent advances have reframed hydroxyurea as a preventive, neuroprotective, and organ-preserving therapy. Early initiation, ideally in infancy, mitigates cumulative tissue injury and preserves long-term function. Children treated before age 5 years have cognitive performance similar to unaffected peers, and the hydroxyurea Prevent trial confirmed reductions in silent cerebral infarcts and vasculopathy with very early use.^{93,94} In parallel, emerging evidence is reshaping views on the effects of hydroxyurea on fertility and pregnancy. Hydroxyurea does not seem to affect spermatogonial pool in males or follicle density in females.^{95,96} Moreover, although prospective data remain scarce, observational studies suggest that continuing hydroxyurea during pregnancy, including beyond the first trimester, might be reasonable in selected women after

careful discussion of risks and benefits.^{97,98} The lack of hydroxyurea-induced mutational effects further supports a higher use for the treatment of sickle cell disease.⁹⁹ Together, these developments support a shift from reactive prescription for recurrent complications to proactive, universal, and preventive therapy across the life course while implementing adequate strategies to improve access and adherence.¹⁰⁰

RBC transfusion

RBC transfusion remains a cornerstone of therapy in sickle cell disease, with established indications in both acute and chronic settings. In fact, while all individuals with sickle cell disease have chronic haemolytic anaemia and most adapt to their steady state low haemoglobin concentration such that anaemia per se is not an indication for blood transfusion, acute exacerbation of chronic anaemia can occur.^{1,2,7} Acute transfusion is used to correct symptomatic anaemia, such as in acute splenic sequestration, transient aplastic crisis, and severe infection-related haemolysis.^{63–66} Exchange transfusion—manual or automated—is preferred for acute organ complications where rapid HbS reduction is required, including acute ischaemic stroke, severe acute chest syndrome, and multiorgan failure, with a goal of reducing HbS to lower than 30% while avoiding hyperviscosity by maintaining total haemoglobin at 9–11 g/dL.^{63–66} Transfusion is also indicated for hepatic sequestration, perioperative optimisation, and in severe sepsis with profound anaemia. Perioperative trials show that transfusion to achieve haemoglobin around 10 g/dL is sufficient, and the TAPS trial showed increased complications without transfusion, establishing preoperative transfusion as the standard of care.¹⁰¹ Chronic transfusion therapy is most firmly established for stroke prevention: the STOP and STOP2 trials confirmed that indefinite transfusion prevents first and recurrent strokes in children with abnormal transcranial Doppler screening velocities,^{18,19} while the SIT trial showed reduced overt strokes in children with silent cerebral infarcts.¹⁰² Additional indications for long-term transfusion include recurrent acute chest syndrome in spite of hydroxyurea therapy, progressive pulmonary hypertension, severe chronic anaemia with organ dysfunction, and selected high-risk scenarios, such as recurrent priapism or early renal disease. Automated exchange transfusion is increasingly favoured in chronic programmes due to superior HbS suppression and lower iron accumulation, although access remains restricted in many settings.

Despite these benefits, RBC transfusion carries important risks.^{103,104} Alloimmunisation is common, reflecting antigenic disparities between predominantly African-ancestry recipients and largely non-African donor pools in Europe and North America, and can result in delayed haemolytic transfusion reactions or hyperhaemolysis, both of which can be life-threatening

and difficult to manage. Best practice includes extended antigen matching (Rh C/c, E/e, and K at minimum), with molecular genotyping increasingly used to reduce alloimmunisation risk. Iron overload is another major complication of chronic transfusion, mandating MRI-based monitoring of liver iron content and timely chelation. Automated exchange can mitigate but not eliminate this burden. In pregnancy, transfusion is not recommended routinely for all women but should be used selectively for maternal or fetal complications (eg, recurrent vaso-occlusive crises, acute chest syndrome, severe anaemia, and intrauterine growth restriction), and for women with previous severe pregnancy morbidity, while prophylactic transfusion remains debated.^{63–66} The TWITCH trial⁹¹ further showed that hydroxyurea can be a safe alternative to chronic transfusion for primary stroke prevention in selected children with abnormal transcranial Doppler velocities after at least 1 year of transfusion therapy. Current guidelines emphasise individualised transfusion planning, regular monitoring, and preferential use of exchange transfusion in high-risk settings, such as stroke prevention.^{63,64,66} In low-resource regions, major challenges include scarce blood availability, insufficient donor screening, and cost, which restrict feasibility. Overall, RBC transfusion remains an essential, life-saving therapy that complements hydroxyurea and curative approaches, providing both acute stabilisation and long-term organ protection when delivered within structured care pathways.

HSCT

HSCT remains the only established cure for sickle cell disease. In children with a human leucocyte antigen (HLA)-matched sibling donor, contemporary programmes report outstanding results: HSCT outcomes by conditioning regimen in paediatric patients with sickle cell disease from the European Bone Marrow Transplantation registry after a median follow-up of 2.7 years showed that 2-year overall survival (OS) was 98.7% (95% CI 90.9–99.8) with busulfan-fludarabine and 99.3% (95% CI 95.2–99.9) with treosulfan-fludarabine.¹⁰⁵ Excellent long-term outcomes, with OS of 95% and an event-free survival rate of 93%, show that HSCT with an HLA-matched sibling donor as a curative option is a role warranted even in young patients.²⁷

In adolescents and adults—where cumulative organ injury limits tolerance of full myeloablation—reduced-intensity or non-myeloablative platforms have broadened eligibility. A recent study in adults showed a 3-year event-free survival of 88.2% and OS of 94.6%, with low rates of graft-versus-host disease (3.5% acute and 0.5% chronic), stable mixed chimerism, and significantly reduced health-care use post-transplant, although graft failure (8.5%) remained a challenge.¹⁰⁶

For patients lacking a matched sibling, donor options continue to expand. Although matched-unrelated and cord-blood HSCT have historically carried higher rates of

graft failure and graft-versus-host disease, refinements (eg, thiotepa-containing conditioning and cord expansion) are improving engraftment and survival.²⁷

The most rapid progress has been with haploidentical transplantation,¹⁰⁷ which offers greater than 90% donor availability across the lifespan and now encompasses several platforms—T-cell-replete bone-marrow grafts with post-transplant cyclophosphamide (often with thiotepa), in vivo T-cell-depleted peripheral blood stem cell aiming for stable mixed chimerism, and ex vivo T-cell receptor- $\alpha\beta$ or CD19-depleted grafts—reporting encouraging early outcomes: the 2-year event-free survival and OS rates were 88.0% (95% CI 73.5–94.8%) and 95.0% (95% CI 81.5–98.7%), respectively. The incidence of grade 3–4 acute graft-versus-host disease at day 100 was 4.8% (95% CI 0.9–14.4%), while the 2-year chronic graft-versus-host disease rate was 22.4% (95% CI 10.9–36.4%) after haploidentical transplantation.¹⁰⁷

Overall, transplant candidacy and regimen intensity should be individualised (eg, age, comorbidity, cerebrovascular disease, or fertility goals) with decisions benchmarked against the benefits and risks of modern disease-modifying therapies and emerging curative options. Several trials are ongoing to explore the optimisation of conditioning regimens for adults and for haploidentical transplantation. In this evolving context, shared decision making and patients' and families' perspectives are crucial to identify the most appropriate treatment for each individual, coupled with long-term evaluation of sickle cell disease-related and HSCT-related morbidity.^{108–111}

New therapies under investigation

New disease-modifying therapies

In recent years, there has been an increase in clinical trials of new therapeutic agents with different mechanisms of action for sickle cell disease, primarily in adults and adolescents. We refer to other reviews for detailed coverage.¹¹² However, despite the commitment of the scientific community, patients and their families, and pharmaceutical companies, progress in the development, approval, and accessibility of new drugs has been disappointing.^{30,31} Inadequate trial endpoints and a lack of consideration of the environmental characteristics and of the differences in health-care organisations across settings might explain the recent failures and the complex multifactorial pathophysiology of sickle cell disease, along with unanticipated safety challenges and regulatory and economic barriers. More efforts are needed not only to ensure the successful implementation of clinical trials, but also to secure regulatory approval, commercialisation, and broad access to these much needed treatments.

Crizanlizumab, L-glutamine, and voxelotor were recently approved by the US Food and Drug Administration after successful trials.^{24–26} The European Medicines Agency did not approve L-glutamine and

	Phase	Primary endpoint	Clinical trial number
Fetal haemoglobin inducers			
Oral decitabine-tetrahydrouridine	2	Change in total haemoglobin at 24 weeks	NCT05405114
Oral decitabine-tetrahydrouridine plus nicotinamide	1	Change in total haemoglobin	NCT04055818
FTX-6058	1	Safety, tolerability, pharmacokinetics, and pharmacodynamics	NCT05169580
BMS-986470	1/2	Safety, tolerability, pharmacokinetics, and pharmacodynamics	NCT06481306
Panobinostat	1	Safety, dose-limiting toxic effects	NCT01245179
GSK4172239D	1	Safety, tolerability, pharmacokinetics, and pharmacodynamics	NCT05660265
ITU512	1/2	Safety and tolerability	NCT06546670
Anti-haemolytic agents			
Vamifeport	2a	Mean change from baseline in haemolysis markers	NCT04817670
GBT021601	2/3	Co-primary endpoints: haemoglobin response (increase from baseline of >1 g/dL); annualised rate of vaso-occlusive crises at week 48	NCT05431088
Pyruvate-kinase activators			
Mitapivat	3	Percentage of participants with haemoglobin response at week 52; annualised rate of pain crises	NCT05031780
Etavopivat	2, open label	Change in cerebral haemodynamics at week 24	NCT05725902
Etavopivat	2, open label	Change in transcranial Doppler velocity	NCT05953584
Etavopivat	2/3	Haemoglobin response rate at week 24 (increase of >1 g/dL [>10 g/L] from baseline); annualised vaso-occlusive crisis rate	NCT04624659
Etavopivat	1/2; children	Pharmacokinetics and safety	NCT06198712
Tebapivat	1	Safety, tolerability, pharmacokinetics, and pharmacodynamics	NCT06924970
Anti-adhesion agents			
Inclacumab	3	Rate of vaso-occlusive crises during the 48-week treatment period	NCT04935879
Individual agents			
Epeleuton (synthetic ω -3 fatty acid)	2	Pharmacokinetics, pharmacodynamics, and safety	NCT05861453
Tadalafil (PDE-5 inhibitor)	2	Change in the recurrence rate of priapism	NCT05142254
HBI-002 (oral carbon monoxide)	2a	Safety	NCT06144749
Tocilizumab (IL-6 inhibitor)	2	Time-weighted pulse oximetry oxygen saturation to fraction of inspired oxygen ratio in patients with acute chest syndrome	NCT05640271
L-citrulline (increase nitric oxide production)	2	Time to crisis resolution	NCT06635902
TAK-755 (recombinant ADAMTS13 enzyme)	1	Safety and development of anti-ADAMTS13 antibodies	NCT03997760
CSL889 (human-derived haemopexin)	2/3	Time to resolution of vaso-occlusive crises	NCT06699849
Oral ketamine	3	Change in pain intensity during vaso-occlusive crises	NCT05378555
Crovalimab (anti-C5 inhibitor)	1b	Safety	NCT04912869
Crovalimab (anti-C5 inhibitor)	2a	Annualised rate of medical facility vaso-occlusive episodes	NCT04912869
Rilzabrutinib (Bcr tyrosine kinase inhibitor)	3	Annualised rate of clinical vaso-occlusive crises	NCT06975865
Ongoing trials by mechanism of action class and individual agents that have different mechanisms of action. The list is not exhaustive and serves as an example.			
Table 4: Ongoing clinical trials with new drugs			

retired the approval of crizanlizumab after dissemination of the results from the STAND trial.¹¹³ Voxelotor was removed from the global market in 2024 for safety concerns. Several drugs targeting different pathophysiological mechanisms of sickle cell disease are currently in various stages of clinical trials and offer promising alternatives for the future (table 4).

New gene therapies

Recent years have seen the emergence of transformative therapies.¹¹⁴ Gene therapy has shifted from experimental proof-of-concept to a licenced therapy for sickle cell disease. Two gene therapies received simultaneous approval in the USA in December, 2023. Lentiviral

β -globin addition (lovo-cel) and CRISPR-Cas9 BCL11A enhancer editing (exagamglogene autotemcel, Casgevy) both achieved high rates of transfusion independence and resolution of vaso-occlusive complications, with approvals subsequently extended to the EU and UK,^{27,28} where the first is not available. Beyond the approved therapies, several gene-editing trials are underway, including the BEACON (autologous base edited CD34+ haematopoietic progenitor stem cells-BEAM-101 [NCT05456880]), CRISPR_SCD001 (NCT03745287), and SAGES1 (NCT06506461) trials. Additional approaches—eg, re-engineered base editors, RNA-interference constructs, and novel lentiviral vectors—are in early development but have not yet entered phases with formal trial listings.

Despite remarkable efficacy, challenges remain, including the reliance on myeloablative conditioning, the risk of insertional mutagenesis and secondary malignancies, manufacturing bottlenecks, and inequitable access in high-burden regions. The next phase of development will focus on less toxic conditioning, in vivo editing, and cost-effective delivery to ensure that curative gene therapies benefit the global sickle cell population.

Recent advances: management in LMICs

One of the most important recent advances globally has been the development of sickle cell disease comprehensive programmes, clinical trials, and data collection systems in LMICs. These achievements are particularly important because LMICs in sub-Saharan Africa and south Asia account for more than 80% of the global burden of sickle cell disease.^{7,10} Health systems in these regions are highly under-resourced with restricted diagnostic capacity, fragmented care pathways, and inadequate access to disease-modifying therapies. In Nigeria and the Democratic Republic of the Congo, 50–90% of children with sickle cell disease die before age 5 years, frequently undiagnosed until late or never diagnosed at all, and without access to basic interventions.^{10,115,116}

The implementation of such programmes has encountered and still faces many challenges. Sickle cell disease is not prioritised in many national health agendas, surveillance systems are weak, registries are scarce, and dedicated funding mechanisms are lacking.¹¹⁷

A systematic and context-adapted approach to improve diagnosis, treatment, and follow-up is urgently needed.

Universal newborn screening and point-of-care testing

Universal newborn screening enables early identification and timely interventions, such as penicillin prophylaxis, vaccinations, and caregiver education. However, in LMICs, fewer than 5% of affected infants are diagnosed within the first year of life.¹¹⁸ Laboratory-based approaches are hindered by logistical delays and resource constraints.

Point-of-care tests, such as HemoTypeSC and Sickle SCAN, show high sensitivity and specificity (>99%), require no electricity, and can be administered by non-laboratory staff.^{119–121} Integration into maternal and child health programmes allows decentralised and scalable implementation¹²² that can improve diagnostic accuracy, reduce late diagnoses, and enhance efforts at premarital screening. The Newborn Screening in Africa initiative has shown feasibility in Ghana, Nigeria, Kenya, Tanzania, Liberia, and Zambia, incorporating family education and linkage to comprehensive care.^{123,124}

Hydroxyurea safety and efficacy in LMICs

Despite the well-known benefit of hydroxyurea for individuals with sickle cell disease, its uptake in LMICs has been limited by concerns regarding infection risk, toxicity, cost, and the need for laboratory monitoring. Hydroxyurea remains underused globally. Among 2145 patients in the global SWAY survey, only 30% reported hydroxyurea use; in Africa, none reported using

	Setting	Population	Study design	Dosing strategy	Key findings
REACH ¹²⁵	Angola, Democratic Republic of Congo, Kenya, Uganda	606 children	Single arm at fixed dose with escalation	15–20 mg/kg per day; mean 17.5±1.8; escalation	Reduced vaso-occlusive crises, infections, malaria, transfusions, and mortality; feasible and safe
NOHARM ¹²⁶	Uganda	207 children	Randomised, double-masked, placebo-controlled	20±2.5 mg/kg per day vs placebo	No increased malaria; improved outcomes; safe in endemic settings
NOHARM MTD ¹²⁷	Uganda	187 children	Randomised fixed vs placebo	Fixed 19.2±1.8 mg/kg vs escalated 29.5±3.6	Dose escalation has superior efficacy; equivalent safety; trial stopped early
SPRING ¹²⁸	Nigeria	220 children	Double-masked, parallel-group, randomised, controlled, phase 3	Fixed low (10 mg/kg) dose vs moderate (20 mg/kg) dose	Both superior to no treatment for primary stroke prevention in case of abnormal transcranial Doppler
SPRINT ¹²⁹	Nigeria	60 children	Double-masked, parallel-group, randomised, controlled, phase 3	Fixed low (10 mg/kg) dose vs moderate (20 mg/kg) dose	Similar recurrence for secondary stroke prevention to SWITCH trial; trial stopped early; hydroxyurea feasible as secondary prevention in settings where transfusion is not feasible
PIVOT ¹³⁰	Ghana	212 children and adults	Double-masked, randomised, placebo-controlled, non-inferiority phase 2 trial	Fixed 20 mg/kg vs placebo in sickle haemoglobin C disease	Similar dose-limiting toxic effects and vaso-occlusive events

NOHARM=Novel use Of Hydroxyurea in an African Region with Malaria trial. NOHARM MTD=NOHARM maximum tolerated dose trial. PIVOT=Prospective Identification of Variables as Outcomes for Treatment trial. REACH=Realizing Effectiveness across Continents with Hydroxyurea trial. SPRING=hydroxyurea for primary stroke prevention in children with sickle cell anaemia in Nigeria trial. SPRINT=Secondary Stroke Prevention Trial in Nigeria trial.

Table 5: Key trials on hydroxyurea use in sub-Saharan Africa

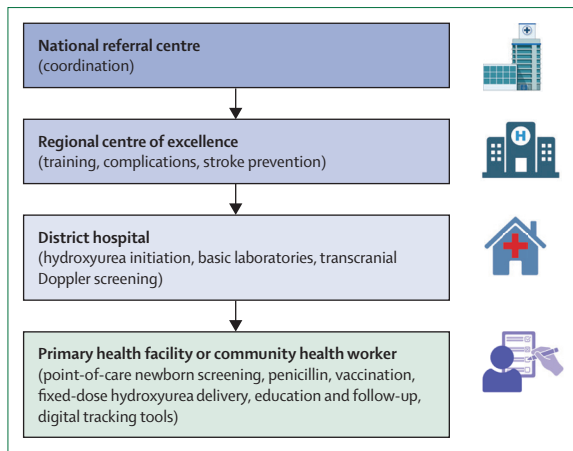


Figure 5: Integrated, decentralised model for sickle cell disease care in low-income and middle-income countries

	Effect	Proposed solution
Delayed or absent diagnosis ^{118-120,123}	High early mortality	Point-of-care testing; national newborn screening programmes
Underuse of hydroxyurea ^{51,125-127,133}	Preventable complications, mortality	Local manufacturing; task-shifting; policy adoption
Lack of transfusion infrastructure ^{128,129,134}	Restricted stroke prevention	Low dose hydroxyurea for stroke prevention
Workforce shortages ^{127,131-133}	Restricted access to care	Nurse-led clinics; community-based care; training networks
Stock-outs and cost barriers ^{51,126,133}	Interrupted treatment	Inclusion in essential medicines lists; pooled procurement
Poor retention and adherence ^{123,124,131,132}	Loss to follow-up	Integration into mother and child health or HIV services; digital reminders and registries

Table 6: Challenges, gaps, and solutions for sickle cell disease care in low-income and middle-income countries

hydroxyurea, reflecting barriers, including scarce availability, high costs, and insufficient monitoring infrastructure.⁵¹ However, several pivotal African studies have addressed these concerns and shown feasibility, safety, and efficacy in reducing the frequency of vaso-occlusive crises and lowering transcranial Doppler screening velocities. Key hydroxyurea trials conducted in Africa are summarised in table 5.¹²⁵⁻¹³⁰

Sickle cell disease care models in LMICs

Delivering sickle cell disease care in LMICs requires decentralised, integrated, and context-adapted models. Reliance on tertiary centres alone cannot achieve broad or equitable coverage. A recent scoping review highlighted that successful programmes integrate into existing health system structures, prioritise

task-shifting, and leverage community health workers for outreach and monitoring.^{131,132} WHO framework suggests a pyramidal, three-level system: primary or community health centres (level 1) for identification, first referral or district hospitals (level 2) for routine care, and secondary or tertiary specialist centres (level 3) for specialised management.¹²⁹ Key strategies include hub-and-spoke networks connecting regional centres to district hospitals and primary facilities;^{116,124,131,132} task-shifting to nurses and community health workers to deliver hydroxyurea, preventive care, and follow-up;^{132,133} and integration with maternal-child health, HIV, immunisation, and nutrition programmes to optimise resources and retention.^{129,130} Embedding sickle cell disease care within the WHO Package of Essential Noncommunicable Disease Interventions (PEN) at the primary level and PEN-Plus at the district level strengthens chronic care management.¹³¹ Digital tools, such as mobile health and telemedicine support monitoring, adherence, and data collection, while national registries enhance surveillance.^{116,124,132} Strengthened transfusion services are essential, requiring reliable supply chains, community donor engagement, and integration into care models, and where transfusion is restricted, hydroxyurea for stroke prevention is crucial.¹³⁴

Capacity building remains fundamental, with sickle cell disease competencies incorporated into medical, nursing, and community curricula, and continuous training delivered via centres of excellence. These tertiary hubs should not function in isolation and should be part of national networks that provide advanced therapies, conduct research, and support training—thereby reducing the need for patients to travel abroad and ensuring more equitable access to comprehensive care. These models are further illustrated in figure 5 and are summarised in table 6.

Controversies

Pregnancy

Pregnancy in sickle cell disease remains high-risk despite structured multidisciplinary care and clearer antenatal pathways. Current guidelines emphasise preconception counselling, integration of fertility services, and intensified surveillance.^{135,136} RBC transfusion is often used but its optimal strategy is unresolved. Previous meta-analyses suggest the benefit of prophylactic transfusion, yet quality of evidence is low and heterogeneous. A recent feasibility randomised controlled trial (TAPS2) showed acceptability and signals of reduced vaso-occlusive crises and preterm birth with serial exchange transfusion, but was underpowered, which underscores the need for a definitive international trial.¹³⁷ Hydroxyurea, the main disease-modifying therapy, is generally discontinued during pregnancy. Emerging cohort and registry data summarised in reviews indicate no clear teratogenic signal but highlight the possible

increased risks of miscarriage, stillbirth, and low birthweight, leaving continuation during gestation uncertain and individualised.^{86,138} Accordingly, when to transfuse and whether or when hydroxyurea can be safely continued remain the principal controversies. Until stronger trial data are available, care should be individualised based on disease severity and obstetric history within specialist multidisciplinary teams, with enrolment in prospective studies encouraged.

Prevention of neurovascular complications

Silent and overt cerebral infarcts remain a major cause of morbidity in sickle cell disease despite early screening and transfusion-based prevention.^{66,67} Abnormal transcranial Doppler screening velocities identify children at risk of overt stroke, but recent cohort studies show that silent infarcts also occur in those with normal transcranial Doppler screening linked to severe anaemia, acute anaemic events, and extracranial carotid arteriopathy. Even with systematic monitoring and disease-modifying therapy, up to one third of children develop silent infarcts, often present at first MRI, underscoring the need for earlier and intensified interventions.^{139–141} Strategies under evaluation include systematic extracranial carotid assessment, earlier use of hydroxyurea, and combining transcranial Doppler screening with magnetic resonance angiography to refine transfusion decisions. Yet, infarcts still occur on hydroxyurea, transfusion remains most effective for vasculopathy, and transplantation can be curative in selected cases. Prevention remains controversial, and broader neurovascular screening and international trials are essential to reduce the lifelong cognitive burden. Ensuring adequate access to screening of neurovascular disease with broad screening coverage and participation into clinical trials of children with cerebral vasculopathy are essential to move forward.

Management of HbSC and HbS-β⁺ disease

Non-HbSS genotypes of sickle cell disease once traditionally regarded as mild, such as HbSC and HbS-β⁺-thalassaemia, are increasingly recognised as clinically heterogeneous conditions associated with considerable morbidity. Recent large registry and cohort studies show that adults with HbSC disease frequently develop complications, such as retinopathy, splenomegaly, avascular necrosis, pulmonary embolism, and acute chest syndrome, with acute care use similar to those with to HbSS.^{142,143} Yet, patients with HbSC remain under-represented in clinical trials, restricting evidence for the efficacy and safety of disease-modifying therapies. Similarly, HbS-β⁺-thalassaemia shows a variable phenotype strongly influenced by the underlying β⁺ mutation. Individuals carrying the IVS-I-110 mutation often have vaso-occlusive crises, splenic sequestration, and stroke, and require transfusion support that resembles HbSS in severity, while those with promoter

mutations can have a milder phenotype.^{35,36} Therefore, optimal management of HbSC and HbSβ⁺ disease remains a major controversy, underscoring the urgent need for genotype-specific research, inclusion in clinical trials, and development of evidence-based standards of care.

Challenges and opportunities: transition from paediatric and adolescent care to adult care

As survival improves with advances in paediatric care, the number of adolescents and young adults with sickle cell disease has grown worldwide.^{20,21,144} This success exposes a crucial gap: the transition from paediatric to adult care remains fragile and poorly coordinated, leading to sharp declines in outcomes. In HICs, mortality rises between ages 18–24 years, with reduced adherence, missed appointments, and inappropriate emergency use.¹⁴⁵ In low-resource settings, challenges are magnified by absent protocols, limited workforce training, and weak follow-up systems. Families, adolescents, and young adults also report distress, loss of trust when leaving familiar paediatric providers, and insufficient preparation for autonomy.¹⁴⁶ Globally, no consensus exists on age cutoffs or care models, despite unique developmental needs. Transition of care is not a simple transfer of records, but a longitudinal process requiring readiness assessments, multidisciplinary collaboration, and health-system accountability.^{146,147} Successful examples from quality networks show that structured approaches can improve outcomes (eg, joint transition clinics, detailed pathways, and adequate education of adolescents, young adults, and families), but implementation remains uneven. As sickle cell disease shifts from a paediatric to a lifelong condition, building equitable and sustainable care transition pathways is an urgent global priority.⁷

Conclusion

Recent decades have seen considerable advances in sickle cell disease management, from universal newborn screening to transformative gene therapy. However, global inequities and fragmented care models persist. As sickle cell disease becomes a lifelong condition, coordinated, multidisciplinary care is crucial. Future clinical trials should incorporate patient-reported outcomes and quality-of-life measures co-developed with patients with sickle cell disease, allowing interventions to address what truly matters to those living with the condition. Implementation science should guide the scaling of proven interventions across diverse health systems, bridging discovery–delivery gaps and informing context-specific strategies that ensure equitable uptake and sustained integration of effective therapies, such as hydroxyurea.^{30,31,148–151} While progress is celebrated, the sickle cell disease community should continue advocating for research funding and improved global access. The next frontier extends beyond curative therapies to embedding equity, personalisation, and integration at every care level.

Contributors

All authors designed the Seminar and wrote the first draft of the manuscript, including the figures and tables. All authors participated in the editing of the manuscript and approved the final version, and all fulfil the authorship requirements as outlined in the International Committee of Medical Journal Editors recommendations.

Declaration of interests

RC received grants or contracts from Vertex and Agios (to institution); payment or honoraria from Global Blood Therapeutics; support for attending meetings and travel from the Physicians' Education Resource; and participated on advisory boards for Vertex, Pfizer, Novo Nordisk, Forma Therapeutics, Global Blood Therapeutics, AddMedica, and Agios. WJ participated on advisory boards for Vertex and Pfizer. JM received grants or contracts from the National Institutes of Health, Gates Foundation, Novartis Institutes for BioMedical Research, European & Developing Countries Clinical Trials Partnership, University of Chicago, and Imperial College London; consulting fees from Pfizer and Tanzania Health Promotion Support; payment or honoraria from Teaching Hematology and the American Society of Hematology; and support for attending meetings and travel from *Annual Reviews Genomics and Human Genetics*, Baylor Tanzania at Texas Children's Hospital, Harvard Medical School, WHO Afro, and Novo Nordisk. BA received payment or honoraria from Accordant and Bain Capital; participated in data safety monitoring boards or advisory boards for Afimmune, Agios Pharmaceuticals, BEAM Therapeutics, bluebird bio, Bristol Myers Squibb, Chiesi, Editas, Fulcrum Therapeutics, Global Blood Therapeutics, Hemanext, Novartis, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi Genzyme, and Vertex; and received grants or contracts from Afimmune, Agios Pharmaceuticals, American Society of Hematology, Connecticut Department of Public Health, Health Resources and Services Administration, Hemanext, National Institutes of Health, Novartis, Novo Nordisk, and Pfizer.

Acknowledgments

We thank Dr Mirco D'Agnolo and Dr Samuela Francescato for the pictures of blood smears presented in figure 1.

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