

Sickle cell disease in children: an update of the evidence in low- and middle-income settings

Isaac Odame^{1,2}

¹Paediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada

²University of Toronto, Toronto, Ontario, Canada

Correspondence to

Professor Isaac Odame, Paediatrics, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Isaac.Odame@SICKKIDS.CA

Received 16 February 2022

Accepted 15 May 2022

ABSTRACT

Sickle cell disease (SCD), one of the most common monogenetic diseases in the world, is associated with multisystemic complications that begin in childhood. Most of the babies homozygous for the sickle haemoglobin gene are born in sub-Saharan Africa. Over the years, progress has been made with early diagnosis through newborn screening, penicillin prophylaxis, pneumococcal immunisation, transcranial Doppler (TCD) screening, hydroxyurea therapy and chronic blood transfusions with remarkably improved survival and quality of life of children with SCD. However, wide disparities in outcomes exist between high-income countries (HICs) where over 90% survive to adulthood, and low-income and middle-income countries (LMICs) where less than half achieve that milestone. Even in HICs, racial inequities pose barriers to accessing specialised care and receiving treatment for acute pain episodes. Better understanding of SCD pathophysiology is being exploited to develop new disease-modifying drugs and gene therapy approaches to further improve outcomes. Bone marrow transplantation is established as a curative treatment for SCD, but it is largely unavailable in LMICs. To bridge the disparity and inequity gaps, innovative approaches are needed in LMICs. Validated and more affordable, easy-to-use point-of-care tests offer opportunities to link early diagnosis with immunisation programmes and healthcare encounters. Widespread use of hydroxyurea therapy—a relatively affordable and effective disease-modifying drug—in LMICs would help improve survival and quality of life. Integration of SCD treatment into primary care linked to district level/provincial hospitals that are supported with evidence-based guidelines will help extend needed interventions to many more patients living in LMICs.

INTRODUCTION

Sickle haemoglobin (HbS) is a structural variant of normal adult haemoglobin caused by a mutation in the β -globin gene (*Glu6Val* in *HBB*) leading to substitution of valine for glutamic acid at position 6 of the β -globin subunit (β^S) of the haemoglobin molecule. Sickle cell disease (SCD), one of the most common monogenetic diseases worldwide, refers to a group of disorders characterised by the presence of at least one β^S allele and a second pathogenic *HBB* variant that results in predominant production of HbS.¹ Its most common form occurs in individuals homozygous for the β^S allele (SCD-SS). Compound heterozygous forms result from co-inheritance with other *HBB* variants including C (SCD-SC), the second most common, and β -thalassaemia (SCD-S β^0 and SCD-S β^+). Co-inheritance

with other genes that encode β -globin chain variants such as D-Punjab, E, O-Arab and Lepore are much rarer forms of SCD. The genotypes SS and S β^0 are further classified as sickle cell anaemia (SCA) as they are associated with the most severe clinical manifestations. The geographical distribution of the β^S allele is mainly driven by the endemicity of malaria from selection pressure due to protection conferred to individuals heterozygous for the β^S allele (sickle trait) against severe *Plasmodium falciparum* malaria.² This accounts for the high prevalence of SCD in sub-Saharan Africa (SSA), India, parts of the Mediterranean, and the Middle East. Population migrations, including the slave trade, explain the wider distribution of the β^S allele to the Americas and Western Europe (figure 1).

Global burden estimates for SCD are steadily improving. Newborn estimates suggest that about 300 000 babies are born with SCA every year. More than 75% of them are born in SSA, with half the global burden shouldered by just three countries: Nigeria, the Democratic Republic of Congo and India.³ It is projected that the annual number of babies born with SCA worldwide will exceed 400 000 by 2050. It has been estimated that 50%–90% of children born with SCA in SSA die before 5 years of age and the WHO has estimated that SCA accounts for up to about 9% of all deaths in children under 5 years in many African countries as SCA is associated with higher risk of mortality from invasive pneumococcal disease (IPD) and malaria.⁴ By contrast, in high-income countries (HICs) with less than 5% of the global disease burden and where newborn screening (NBS) and early interventions with comprehensive care are routinely practised, over 95% of children born with SCD survive beyond 18 years of age^{5 6} (table 1).

Public health improvements targeted at reducing under-5 years mortality in low-income and middle-income countries (LMICs) have indirectly enabled improved prevention and treatment of some SCD-associated morbidities (eg, IPD and malaria) causing an epidemiological transition whereby some children with SCA who would have died undiagnosed in early life now survive. Thus, the number of people living with SCD is expected to increase both in HICs and LMICs.⁷

PATHOLOGY AND CLINICAL MANIFESTATIONS

SCD is a multisystemic disorder that can affect nearly every organ resulting in acute and chronic complications. The indispensable pathophysiological event is polymerisation of HbS. Intracellular polymerisation changes the shape and physical properties of the erythrocytes (sickle erythrocytes)



© Author(s) (or their employer(s)) 2022. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Odame I. *Arch Dis Child* Epub ahead of print: [please include Day Month Year]. doi:10.1136/archdischild-2021-323633

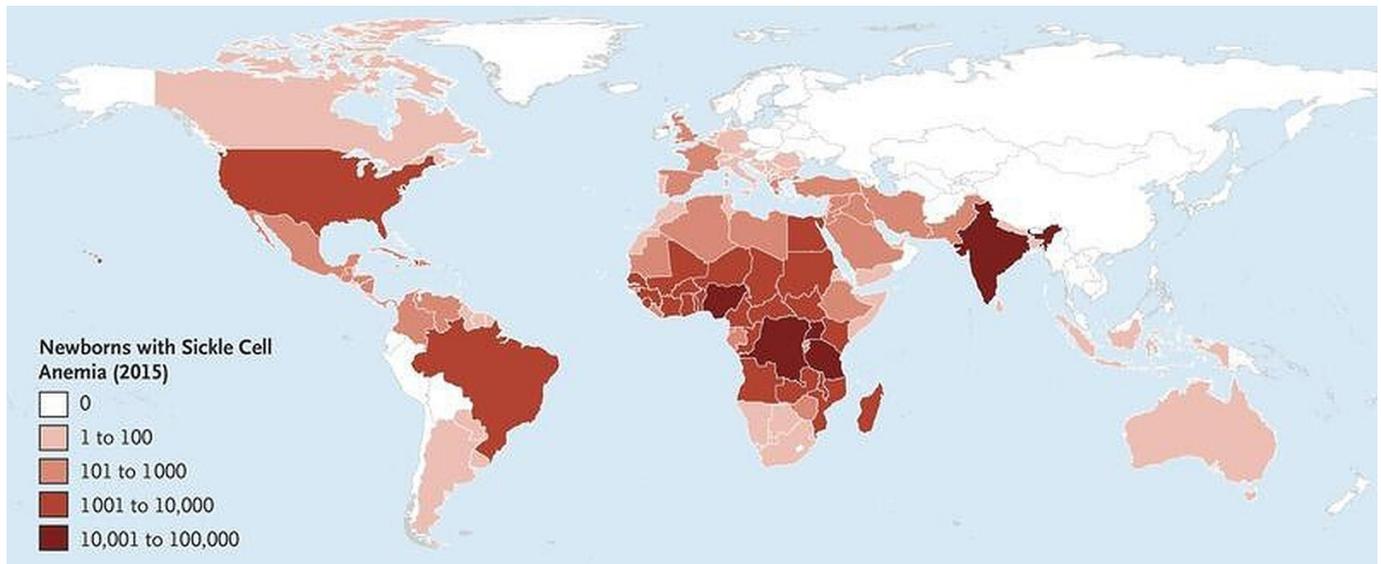


Figure 1 Number of newborns with sickle cell anemia in each country in 2015. Data are based on estimates from Piel *et al.* Alaska is shown separately from the rest of the USA.⁴¹

making them less deformable with abnormal rheological features and expression of adhesion molecules. This results in circulatory sludging with occlusion of blood flow from adherent sickle erythrocytes and white cells at the level of capillaries and post-capillary vessels (vaso-occlusion), and haemolysis. In addition, vascular endothelial activation and injury resulting from functional nitric oxide deficiency, inflammatory mediators, excess oxidant generation and reperfusion, hypercoagulability, and platelet activation, ultimately cause tissue injury and end-organ damage.⁸ Vaso-occlusion typically causes ischaemic damage to tissues resulting in severe pain (vaso-occlusive pain episodes) and other acute complications including hyposplenism-related infections, acute chest syndrome (ACS), splenic sequestration, stroke and priapism. Chronic anaemia, cerebrovascular damage, kidney disease, pulmonary hypertension, avascular necrosis

of bone, retinopathy and gallstones are some of the chronic complications of SCD.⁹ It is important to note that infants and young children with SCD may not have any history of symptoms until they present with acute illness such as infection that can result in death. Early signs of SCD include dactylitis (hand-foot syndrome), pallor, jaundice and splenomegaly. Children with milder forms of SCD may not show any physical signs of SCD throughout their childhood.

EARLY DIAGNOSIS AND MANAGEMENT

Laboratory techniques used for the diagnosis of SCD are based on biochemical methods that enable separation of haemoglobin species according to their protein structure and electrical charge, including haemoglobin electrophoresis, isoelectric focusing,

Table 1

Sickle cell anaemia: existing disparities between HICs and LMICs

	HICs NBS, early diagnosis and comprehensive care available	LMICs NBS, early diagnosis and comprehensive care not commonplace.
		Late presentation with acute SCD complications and high mortality.
	Disease-modifying therapies more available	Disease-modifying treatments (hydroxyurea and chronic blood transfusions) not widely available or affordable
	Racial inequalities exist in high-resource settings relating to: ▶ access to primary and specialised care ▶ barriers to receiving pain treatment	SCD diagnosis and care not linked to primary care, and limited numbers of SCD centres in district hospitals
	Fewer health workers with knowledge and expertise in SCD management	Lack of universal health coverage for SCD diagnosis and treatment
	Challenges with transition from paediatric to adult care	Inadequate public awareness about SCD and the effective interventions available

HICs, high-income countries; LMICs, low-income and middle-income countries; NBS, newborn screening; SCD, sickle cell disease.

capillary electrophoresis, high-performance liquid chromatography and mass spectroscopy. These methods determine the types of haemoglobin present in the red cells but cannot establish the haemoglobin genotype inherited by an individual. 'Sickling' or 'Solubility' tests do not distinguish between the clinically benign sickle cell trait from various forms of SCD when 'positive'. They should not be used to test newborns up to 6 months of age as the high haemoglobin F (HbF) and low HbS will give false-negative results. Where they are available, DNA-based testing is employed by specialised labs in prenatal diagnosis of SCD and analyses of specific haemoglobin variants associated with rare forms of SCD. Point-of-care (POC) tests for SCD based on immunoassay or micro-engineered electrophoretic methods have been developed.^{10 11} They can be useful for screening newborns (immunoassay) and infants over 4 weeks of age (micro-electrophoresis). Their favourable characteristics, including lower cost, rapid, portable, and high sensitivity and specificity for detecting the common forms of SCD make them attractive for use in low-resource settings.

Advances in paediatric care, early diagnosis and comprehensive treatment have led to improved outcomes for children with SCD in HICs. In LMICs, the high disease burden is exacerbated by inadequate healthcare infrastructure, poor nutrition and infectious comorbidities like malaria and HIV, leading to poorer outcomes. Comprehensive management of SCD in childhood should include strategies for early diagnosis through NBS programmes, health maintenance and management of acute and chronic complications using the available resources, and involving the patients and their families in medical decision-making. This review on SCD provides an update of the evidence based on systematic reviews and recommendations formulated using the Grading of Recommendations Assessment, Development and Evaluation approach to assess the certainty in the evidence. For LMICs without resources to implement the evidence-based strategies, the best available evidence is discussed to help inform the development of guidelines for the management of children with SCD relevant to district-level/provincial hospitals (table 2).

Infection prevention

Invasive pneumococcal disease

Infants and children with SCA have a very high risk of IPD (bacteraemia and meningitis) due to reduced or absent splenic function that typically begins in the first few years of life. IPD in children with SCA has a high case-fatality rate. A meta-analysis of three randomised controlled trials (RCTs) and one observational study showed that prophylactic penicillin therapy reduces the risk of IPD in children with SCD-SS.^{12–15} Evidence is lacking for children with genotypes other than homozygous S (SS). One trial that evaluated the consequences of discontinuing penicillin prophylaxis suggested that prophylaxis in children who have not had prior IPD, or a splenectomy may be discontinued at 5 years of age. A meta-analysis of seven studies in SSA found an increased prevalence of SCD in children with IPD compared with those without IPD. Vaccination against *Streptococcus pneumoniae* is strongly recommended for children with SCD at all ages.¹⁶ The implementation of universal early childhood immunisation with pneumococcal conjugate vaccines in low-income countries (LICs) has reduced the incidence of IPD in children with SCD through herd immunity. Nevertheless, reports of cases of IPD from non-vaccine serotypes support recommendations to implement both penicillin prophylaxis and antipneumococcal vaccinations in children with SCD.

Malaria

Several studies have shown that individuals with SCD living in malaria-endemic regions have some protection against malaria, with lower prevalence of infection and lower parasite density compared with non-SCD children.¹⁷ However, mortality from malaria is significantly higher in parasitaemic children with SCD.¹⁸

There is ongoing debate regarding the appropriate agent to use for chemoprophylaxis. Current practice in malaria-endemic countries varies but involves use of insecticide-treated nets, chemoprophylaxis during high-transmission seasons, and prompt diagnosis and treatment of malaria.

Screening for pulmonary disease

Respiratory conditions such as asthma are associated with increased risk of morbidity and mortality in children with SCD. Pulmonary function tests (PFTs) have demonstrated obstructive and restrictive patterns in children and adolescents with SCD. A number of longitudinal and cross-sectional studies described results of screening with PFTs in children with SCD who had no respiratory symptoms compared with control groups without SCD, but none discussed any type of interventions. No study evaluated the utility of screening with PFT versus no screening in children with SCD. A consensus panel recommended that children with SCD should be screened for respiratory symptoms by history and examination. Those found to have signs or symptoms of respiratory disease should undergo further assessment, including PFTs, to determine the cause and treatment plan.¹⁹

Screening for pulmonary hypertension

Echocardiography evaluation to estimate pulmonary arterial hypertension using tricuspid regurgitant velocity (TRV) has shown that elevated TRV is associated with increased risk for all-cause mortality in adults with SCA, but no studies have shown a mortality risk in children.¹⁹ The utility of echocardiography as a screening tool for pulmonary hypertension in asymptomatic individuals is not clear.

Hydroxyurea therapy for preventing exacerbations

Hydroxyurea (also called hydroxycarbamide), a ribonucleotide reductase inhibitor, was identified as a drug candidate to increase HbF levels in people with SCD following documentation of the beneficial effects of persistent elevations of HbF in cohort studies conducted over 40 years ago. The first RCT of hydroxyurea therapy in patients with SCA was conducted in adults with severe clinical disease, demonstrating efficacy for reducing acute pain episodes, ACS, need for blood transfusions and hospitalisations.²⁰ Later, an RCT in children and young adults with SCA aged 2–22 years and with severe clinical disease showed reduced number of hospitalisations as well as days of hospitalisation.²¹ Another RCT in children with SCA was conducted to determine the effect of hydroxyurea on organ function and clinical complications in children, who initiated hydroxyurea or placebo treatment at age 9–18 months regardless of clinical severity. While significant differences were not seen in measures of spleen function and glomerular filtration rate, hydroxyurea therapy decreased acute pain episodes, dactylitis, ACS, hospitalisation rates and transfusions compared with placebo.²² Only one RCT has been conducted in SSA, the ethical basis of which was grounded in the need to know whether hydroxyurea therapy is associated with increased risk for clinical malaria in children living in malaria-endemic regions. Children with SCA aged 1–4 years were enrolled if they lived within 50 km of the

Table 2

Summary of evidence-based interventions for children and adolescents with SCA

Interventions	Recommendations	Strength of recommendation	Certainty in evidence
Infection prevention			
Penicillin prophylaxis	Prophylactic penicillin therapy should be given until age 5 years in children with SCD-SS	Strong	Moderate
	In children with SCD-SS who have not had prior IPD or splenectomy and have completed the recommended pneumococcal vaccination series, prophylactic penicillin can be discontinued	Weak	Moderate
Pneumococcal vaccination	All children with SCD should be vaccinated against <i>Streptococcus pneumoniae</i>	Strong	Moderate
Malaria prevention	Children with SCD in malaria endemic areas should receive prophylaxis against malaria	Strong	Low
Management of acute complications			
Vaso-occlusive pain episodes	The WHO strategy recommends acetaminophen together with ibuprofen (an NSAID) for mild pain, and a strong opioid (morphine as first choice) for moderate-to-severe pain.	Strong	Low
	A short course (5–7 days) of NSAIDs in addition to opioids is recommended for acute SCD pain management	Conditional	Low
	A systematic review of the evidence recommends against using chronic monthly transfusion therapy as first-line strategy to prevent recurrent acute pain episodes	Conditional	Low
Acute chest syndrome	Treat children with SCD who have ACS with an intravenous cephalosporin, an oral macrolide, supplemental oxygen (to maintain saturation >95%) and close monitoring for bronchospasm, acute anaemia and hypoxaemia	Strong	Low
	Give simple blood transfusion to improve oxygen-carrying capacity to children with moderately symptomatic ACS whose haemoglobin >10 g/L below baseline. If base haemoglobin \geq 90 g/L, blood transfusion may not be required	Conditional	Low
	Perform urgent exchange transfusion when, despite simple transfusion, there is rapid progression of ACS with oxygen saturation <90% despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates and/or decline in haemoglobin levels	Conditional	Low
Acute treatment of suspected or confirmed stroke	For children with SCD and acute neurological deficits including TIA prompt blood transfusion is recommended. The transfusion should be given immediately on recognition of symptoms without delay beyond 2 hours of acute neurological symptom presentation. The type of transfusion (simple or exchange blood transfusion) is dependent on individual patient factors and local transfusion resources	Strong	High
	For children with SCD and acute neurological deficits including TIA, exchange blood transfusion (EBT) is recommended versus simple blood transfusion. When exchange blood transfusion is not available within 2 hours and haemoglobin is <85 g/L, simple blood transfusion can be performed to avoid delays in treatment while EBT is planned	Moderate	Low
Stroke prevention			
Primary stroke prevention	Children with SCA who have abnormal TCD screening should receive regular blood transfusions given every 3–4 weeks aimed to maintain HbS level <30% and haemoglobin level >90 g/L and <130 g/L.	Strong	Moderate
	For children with SCA who have abnormal TCD screening and live in LMICs, where regular transfusions and chelation therapy are not available or affordable, hydroxyurea therapy with dose ranging from 20 mg/kg/day to maximum tolerable dose is recommended	Strong	Low
Secondary stroke prevention	For children with SCA and a history of prior stroke regular blood transfusion with goals to increase haemoglobin >90 g/L and maintaining HbS level at <30% is recommended	Strong	Low
	In LMICs where regular transfusion therapy is not available or affordable, hydroxyurea therapy is an alternative—inferior to transfusion therapy but better than no therapy at all for secondary stroke prevention.	Strong	Low
Hydroxyurea therapy	Children with SCA who have severe disease (recurrent pain, dactylitis, ACS and anaemia) should be treated with hydroxyurea.	Strong	High
	Infants 9 months or older, children and adolescents with SCA should be offered hydroxyurea therapy regardless of clinical severity (depending on patients' or families' values, drug availability and costs) to prevent SCA-related complications.	Strong	Moderate
	For children with SCA who need primary and secondary stroke prevention in LMICs where regular transfusions and chelation therapy are not available or affordable, hydroxyurea therapy is recommended.	Strong	Low
Screening for chronic complications			
Pulmonary disease	Children with SCD with no respiratory symptoms should not be screened with pulmonary function tests.	Conditional	Low
Pulmonary hypertension	Screening asymptomatic children with SCD for pulmonary hypertension using echocardiography is not recommended.	Conditional	Low

ACS, acute chest syndrome; HbS, sickle haemoglobin; IPD, invasive pneumococcal disease; LMICs, low-income and middle-income countries; SCA, sickle cell anaemia; SCD, sickle cell disease; TCD, transcranial Doppler; TIA, transient ischaemic attack.

clinic, regardless of clinical severity. Malaria incidence did not differ between children on hydroxyurea or placebo. In addition, a composite SCA-related clinical outcome (acute pain episode, dactylitis, ACS, splenic sequestration or blood transfusion) was less frequent with hydroxyurea than placebo.²³ All the RCTs in children demonstrated clinical and laboratory benefits (increased haemoglobin concentration and HbF, with decreased leucocytes and reticulocytes) without increase in adverse events.

Given the limited resources for chronic blood transfusions and bone marrow transplantation in LMICs, hydroxyurea therapy remains the only disease-modifying therapy feasible for widespread use in these regions.

Prevention of vaso-occlusive pain episodes

Acute SCD pain, also referred to as vaso-occlusive crisis is the most common acute manifestation of SCD. Most common sites in children are the extremities, chest and lower back, and usually there is no clear precipitating activity. Dactylitis (hand-foot syndrome), a painful swelling of the hands and feet, is often the first episode in infants and toddlers with SCD. Acute SCD pain may occur concurrently with other acute complications of SCD such as ACS and infections. No biomarkers or imaging studies can confirm SCD pain, therefore, pain management must be guided by patient or family report of the severity of pain. The

WHO two-step strategy for pharmacological management of pain in children is a good guide for clinicians caring for children with SCD.

A systematic review to evaluate the role of non-opioid pharmacological agents in the treatment of acute SCD pain found low-to-moderate benefits of NSAIDs, including improved pain control, reduced opioid utilisation and decreased length of stay in hospital. Balancing these benefits against potential risks, such as nephrotoxicity and gastrointestinal bleeding, the review favoured use of NSAIDs.²⁴

Three RCTs of chronic blood transfusion treatment for recurrent SCD pain in children showed decreased rates of acute pain episodes, but the evidence is of low certainty as participants were enrolled for other indications for transfusion (abnormal TCD ultrasound, stroke and silent stroke).^{25–27} Monthly blood transfusions are associated with moderate risk of harm (iron overload, bloodborne infections, alloimmunisation and transfusion reactions) and a very high burden (monthly visits, chelation therapy, intravenous access issues, limited blood availability in LMICs and high costs).

Management of ACS

ACS is a pneumonia-like complication of SCD associated with fever, chest pain, cough, shortness of breath, wheezing, retractions and a new pulmonary infiltrate on chest radiograph. ACS is a common cause of hospitalisation and one of the leading causes of death in children with SCD; therefore, early recognition and treatment are crucial.²⁸ ACS can develop rapidly progressing from a mild-to-severe respiratory illness (with significant decline in haemoglobin and/or oxygen saturations) requiring ventilatory support. The most common defined aetiology is infection (viral, bacteria, mycoplasma or chlamydia) and others include fat embolism, atelectasis or intrapulmonary aggregates of sickle cells. Interventions may include antibiotics, supplemental oxygen, respiratory support, bronchodilators and blood transfusions.²⁹ The overall quality of evidence in support of each of these interventions is low. But, given the pathophysiology of ACS, a combination of these supportive interventions is recommended depending on the severity of ACS. There is a lack of comparison between the efficacy of exchange blood transfusion versus simple transfusion or between blood transfusion and no blood transfusion. But the degree of beneficial effects of exchange blood transfusion or simple transfusion is likely to be proportional to the severity of ACS.

Prevention and management of cerebrovascular disease

Stroke is one of the most devastating complications of SCD in children, more common in SCD-SS than other types of SCD. It may be clinically silent or overt (ischaemic, haemorrhagic or transient ischaemic attack) and associated with significant cognitive impairments. The highest incidence of stroke is in children with SCD-SS, 2–9 years of age. A major therapeutic objective in the management of SCD in children should focus on primary stroke prevention, acute and timely treatment of suspected or confirmed stroke, and secondary prevention of strokes in children with a prior history of stroke. A systematic review identified three RCTs that demonstrated the efficacy of transfusion in children with SCA and abnormal TCD velocities.^{30–33} One RCT of hydroxyurea therapy in children with SCA in Nigeria demonstrated efficacy of both low-dose and moderate-dose hydroxyurea therapy in lowering stroke incidence.³⁴

Children with SCA and overt strokes have ongoing risk for stroke recurrence. One RCT found hydroxyurea at maximum

tolerated dose combined with phlebotomy to be inferior to continuing transfusion with ongoing iron chelation therapy.³⁵ Two retrospective cohort studies and a prospective multi-centre trial provide evidence that regular blood transfusion therapy is partially effective for secondary stroke prevention in children with SCA in those who received blood transfusion versus historical controls who had strokes and did not receive blood transfusions. Further evidence shows that regular blood transfusion therapy is superior to hydroxyurea therapy, but hydroxyurea therapy is better than no treatment at all for secondary stroke prevention.³³

MANAGEMENT IN LMICS

NBS programmes are effective because they enable early diagnosis and initiation of simple life-saving interventions such as penicillin prophylaxis, pneumococcal vaccination, parental education and prompt management of febrile illness. But they are limited in LMICs as the infrastructure for centrally coordinated NBS is not available. However, the diagnosis gap can be largely bridged by employing more affordable POC devices for screening in the context of existing immunisation clinics and other healthcare encounters. Early diagnosis in primary care settings can be followed by referral to SCD clinics in district hospitals for delivery of health maintenance and disease-modifying treatments.

With the limited resources in LMICs to administer chronic blood transfusions, iron chelation therapy and curative haematopoietic stem cell transplantation (HSCT), hydroxyurea therapy is the most feasible disease-modifying treatment for SCA to reduce pain episodes, dactylitis, ACS, severe anaemia and need for blood transfusions and hospitalisations, and to prevent strokes (table 3).

Programmes for effective SCD management should be linked to SCD prevention programmes that include public awareness, genetic counselling, premarital testing and counselling and development of few specialised centres for prenatal and preimplantation genetic diagnosis. LMICs need to train more genetic counsellors to provide genetic education that empowers at-risk partners to make informed decisions in the context of their cultural norms and religious beliefs.

Emerging disease-modifying and curative therapies

Until 2017, only two disease-modifying therapies (hydroxyurea and blood transfusions) for SCD were available. Since then, three agents, L-glutamine, crizanlizumab (a P-selectin blocking monoclonal antibody) and voxelotor (small molecule that reduces HbS polymerisation) have received approval in some countries, although their postmarketing effectiveness is yet to be demonstrated.^{36–38} Several other pharmacological agents for disease-modifying treatment of SCD are in the development pipeline.

HSCT is currently the only established curative treatment for SCD. However, its use has been limited in HICs by the availability of suitably matched sibling donors, procedure-related toxicities and costs, and in LMICs by availability of transplant centres. Donor sources are now being expanded by using haploidentical donors and transplant-related toxicities reduced by employing reduced-intensity conditioning regimens and better graft-versus-host disease prevention/treatment strategies. Though HSCT is widely available in HICs, inequities exist in their accessibility for treating patients with SCD.

Table 3 Management of sickle cell anaemia in HICs and LMICs

	HICs	LMICs
NBS and early intervention	Universal NBS programme includes SCD	No universal NBS system Standalone local SCD screening programmes POC testing ▶ Linked to immunisation clinics and primary health centres ▶ During healthcare encounters
	Penicillin prophylaxis	Penicillin prophylaxis Malaria prophylaxis
	Pneumococcal immunisation	Pneumococcal vaccines- ▶ Global Alliance for Vaccines and Immunisation (GAVI) supported primary PCV
	Splenic palpation Fever and pain management Parental/family education	Splenic palpation Fever and pain management Parental/family education Integration into primary healthcare
Comprehensive care	TCD screening ▶ Primary stroke prevention Hydroxyurea therapy Chronic blood transfusion Exchange blood transfusion Haematopoietic stem cell transplant	TCD testing if available Hydroxyurea therapy ▶ Primary stroke prevention ▶ Widespread use beneficial in the absence of routine TCD testing Nutritional support
	Acute care ▶ Acute pain episodes ▶ Sepsis ▶ Acute chest syndrome ▶ Acute splenic sequestration ▶ Acute stroke	Acute care ▶ Acute pain episodes ▶ Sepsis and malaria ▶ Acute chest syndrome ▶ Acute severe anaemia ▶ Acute splenic sequestration ▶ Acute stroke
	Health maintenance ▶ SCD centres linked to lower levels of care ▶ Screening for cerebrovascular disease MRI and Magnetic Resonance Angiography (MRA), retinopathy, renal disease ▶ Psychosocial support of patient/family	Health maintenance ▶ SCD clinics in district hospitals linked to primary and tertiary levels of care ▶ Screening for cerebrovascular disease using validated clinical tools (if MRI/MRA not available), retinopathy, renal disease ▶ Psychosocial support of patient/family
	Prevention of SCD	Public awareness and education ▶ Engagement of community leaders
Prevention of SCD	Awareness in at-risk population	Public awareness and education ▶ Engagement of community leaders
	Genetic counselling	Training of genetic counsellors ▶ Improve access to genetic counsellors
	Premarital testing and counselling Prenatal diagnosis PGD	Premarital testing and counselling Prenatal diagnosis and PGD (not widely available)

HICs, high-income countries; LMICs, low-income and middle-income countries; NBS, newborn screening; PCV, pneumococcal conjugate vaccine; PGD, preimplantation genetic diagnosis; POC, point-of-care; SCD, sickle cell disease; TCD, transcranial Doppler.

Gene therapy approaches based on gene modification of autologous haematopoietic stem cells are currently undergoing clinical trials. These strategies include gene addition (mediated by lentiviral vectors) and genome editing (*eg*, Clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) to modify or replace the defective sickle gene or induce high HbF expression.^{39 40} With these therapies, the barrier posed by limited availability of matched sibling donors is removed as no donor is required, making more patients eligible for treatment.

Correction notice This paper has been modified since it was first published. The title has been corrected to more accurately reflect the content. One further reference to WHO has been removed to avoid potential misattribution regarding WHO's involvement with this article.

Twitter Isaac Odame @DrOdame

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Map disclaimer The inclusion of any map (including the depiction of any boundaries therein), or of any geographic or locational reference, does not imply the expression of any opinion whatsoever on the part of BMJ concerning the legal status of any country, territory, jurisdiction or area or of its authorities. Any such expression remains solely that of the relevant source and is not endorsed by BMJ. Maps are provided without any warranty of any kind, either express or implied.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

- Bunn HF. Pathogenesis and treatment of sickle cell disease. *N Engl J Med Overseas Ed* 1997;337:762–9.
- Piel FB, Patil AP, Howes RE, *et al*. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. *Nat Commun* 2010;1:104.
- Piel FB, Hay SI, Gupta S, *et al*. Global burden of sickle cell anaemia in children under five, 2010–2050: modelling based on demographics, excess mortality, and interventions. *PLoS Med* 2013;10:e1001484.
- Grosse SD, Odame I, Atrash HK, *et al*. Sickle cell disease in Africa: a neglected cause of early childhood mortality. *Am J Prev Med* 2011;41:S398–405.
- Telfer P, Coen P, Chakravorty S, *et al*. Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London. *Haematologica* 2007;92:905–12.
- Quinn CT, Rogers ZR, McCavit TL, *et al*. Improved survival of children and adolescents with sickle cell disease. *Blood* 2010;115:3447–52.
- Global Burden of Disease Pediatrics Collaboration, Kyu HH, Pinho C, *et al*. Global and national burden of diseases and injuries among children and adolescents between 1990 and 2013: findings from the global burden of disease 2013 study. *JAMA Pediatr* 2016;170:267–87.

- 8 Manwani D, Frenette PS. Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies. *Blood* 2013;122:3892–8.
- 9 Heibel R, Vercellotti G, Nath K. A systems biology consideration of the vasculopathy of sickle cell anemia: the need for multi-modality chemoprophylaxis. *Cardiovasc Hematol Drugs Targets* 2009;9:271–92.
- 10 McGann PT, Hoppe C. The pressing need for point-of-care diagnostics for sickle cell disease: a review of current and future technologies. *Blood Cells Mol Dis* 2017;67:104–13.
- 11 Alapan Y, Fraiwan A, Kucukal E, et al. Emerging point-of-care technologies for sickle cell disease screening and monitoring. *Expert Rev Med Devices* 2016;13:1073–93.
- 12 Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. *N Engl J Med* 1986;314:1593–9.
- 13 Falletta JM, Woods GM, Verter JI, et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia. prophylactic penicillin study II. *J Pediatr* 1995;127:685–90.
- 14 John AB, Ramlal A, Jackson H, et al. Prevention of pneumococcal infection in children with homozygous sickle cell disease. *Br Med J* 1984;288:1567–70.
- 15 John AB, Ramlal A, Jackson H, et al. Prevention of pneumococcal infection in children with homozygous sickle cell disease. *BMJ* 1984;288:1567–70.
- 16 Ramakrishnan M, Moisi JC, Klugman KP, et al. Increased risk of invasive bacterial infections in African people with sickle-cell disease: a systematic review and meta-analysis. *Lancet Infect Dis* 2010;10:329–37.
- 17 Aluoch JR. Higher resistance to Plasmodium falciparum infection in patients with homozygous sickle cell disease in Western Kenya. *Trop Med Int Health* 1997;2:568–71.
- 18 Makani J, Komba AN, Cox SE, et al. Malaria in patients with sickle cell anemia: burden, risk factors, and outcome at the outpatient clinic and during hospitalization. *Blood* 2010;115:215–20.
- 19 Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA* 2014;312:1033–48.
- 20 Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the multicenter study of hydroxyurea in sickle cell anemia. *N Engl J Med* 1995;332:1317–22.
- 21 Ferster A, Vermeylen C, Cornu G, et al. Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. *Blood* 1996;88:1960–4.
- 22 Wang WC, Ware RE, Miller ST, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (baby Hug). *Lancet* 2011;377:1663–72.
- 23 Opoka RO, Ndugwa CM, Latham TS, et al. Novel use of hydroxyurea in an African region with malaria (NOHARM): a trial for children with sickle cell anemia. *Blood* 2017;130:2585–93.
- 24 Brandow AM, Carroll CP, Creary S, et al. American Society of hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood Adv* 2020;4:2656–701.
- 25 Alvarez O, Yovetich NA, Scott JP, et al. Pain and other non-neurological adverse events in children with sickle cell anemia and previous stroke who received hydroxyurea and phlebotomy or chronic transfusions and chelation: results from the switch clinical trial. *Am J Hematol* 2013;88:932–8.
- 26 DeBaun MR, Gordon M, McKinsty RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. *N Engl J Med* 2014;371:699–710.
- 27 Miller ST, Wright E, Abboud M, et al. Impact of chronic transfusion on incidence of pain and acute chest syndrome during the stroke prevention trial (stop) in sickle-cell anemia. *J Pediatr* 2001;139:785–9.
- 28 Vichinsky EP, Styles LA, Colangelo LH, et al. Acute chest syndrome in sickle cell disease: clinical presentation and course. Cooperative study of sickle cell disease. *Blood* 1997;89:1787–92.
- 29 Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National acute chest syndrome Study Group. *N Engl J Med* 2000;342:1855–65.
- 30 Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med* 1998;339:5–11.
- 31 Adams RJ, Brambilla D, Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) Trial Investigators. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. *N Engl J Med* 2005;353:2769–78.
- 32 Ware RE, Davis BR, Schultz WH, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial Doppler flow velocities in children with sickle cell anaemia-TCD with transfusions changing to hydroxyurea (twitch): a multicentre, open-label, phase 3, non-inferiority trial. *Lancet* 2016;387:661–70.
- 33 DeBaun MR, Jordan LC, King AA, et al. American Society of hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. *Blood Adv* 2020;4:1554–88.
- 34 Abdullahi SU, Jibir BW, Bello-Manga H, et al. Hydroxyurea for primary stroke prevention in children with sickle cell anaemia in Nigeria (spring): a double-blind, multicentre, randomised, phase 3 trial. *Lancet Haematol* 2022;9:e26–37.
- 35 Ware RE, Helms RW, SWITCH Investigators. Stroke with transfusions changing to hydroxyurea (switch). *Blood* 2012;119:3925–32.
- 36 Niihara Y, Smith WR, Stark CW. A phase 3 trial of L-glutamine in sickle cell disease. *N Engl J Med* 2018;379:226–35.
- 37 Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med* 2017;376:429–39.
- 38 Vichinsky E, Hoppe CC, Ataga KI, et al. A phase 3 randomized trial of Voxelotor in sickle cell disease. *N Engl J Med* 2019;381:509–19.
- 39 Ribeil J-A, Hacein-Bey-Abina S, Payen E, et al. Gene therapy in a patient with sickle cell disease. *N Engl J Med* 2017;376:848–55.
- 40 Frangoul H, Altshuler D, Cappellini MD, et al. Crispr-Cas9 gene editing for sickle cell disease and β -thalassaemia. *N Engl J Med* 2021;384:252–60.
- 41 Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med* 2017;376:1561–73.