WHO consolidated guidelines for the management of common childhood illness

Management of sickle-cell disease in children and adolescents

World Health Organization

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ISBN 978-92-4-012266-6 (electronic version)
ISBN 978-92-4-012267-3 (print version)

Suggested citation. WHO consolidated guidelines for the management of common childhood illness: management of sickle-cell disease in children and adolescents. Geneva: World Health Organization; 2026. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at https://iris.who.int/.

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Graphic design and layout: Trans.Lieu Company Ltd

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Acknowledgements

The guidelines for the management of sickle-cell disease in children and adolescents were prepared by the World Health Organization (WHO) Department of Sexual, Reproductive, Maternal, Child and Adolescent Health and Ageing. Other departments represented on the WHO Steering Group include: the Department for HIV, Tuberculosis, Hepatitis, Sexually Transmitted Infections; the Department of Nutrition and Food Safety; Malaria and Neglected Tropical Diseases; Science for Health; the Department of Noncommunicable Diseases and Mental Health; and the Department of Medicines and Health Products Policies and Standards.

WHO wishes to express its gratitude to the following Guideline Development Group members, the external reviewers, the guidelines methodologists and the institutions that conducted the systematic reviews for their contributions to the development of the guidelines:

Guideline Development Group

WHO thanks the Guidelines Development Group members who reviewed the evidence and made these recommendations: Mohamed Ahmed Abdullah, University of Khartoum, Khartoum, Sudan; Adekunle Adekile, Kuwait University, Kuwait City, Kuwait; Shams El Arifeen, International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh; Uma Athale, McMaster University, Hamilton, Canada; Gillian Birchwood, The Queen Elizabeth Hospital, Bridgetown, Barbados; Trevor Duke, University of Melbourne, Faculty of Medicine, Dentistry and Health Sciences, Melbourne, Australia; Michael (Mike) English, University of Oxford, Oxford, United Kingdom of Great Britain and Northern Ireland; Jane Hankins, St. Jude Children's Research Hospital, Tennessee, United States of America; Grace Irimu, University of Nairobi, Nairobi, Kenya; Phillip Kasirye, Makerere University College of Health Sciences, Kampala, Uganda; Shanzida Khatun, National Institute of Advanced Nursing Education and Research, Dhaka, Bangladesh; Ajay Khera, EngenderHealth, New Delhi, India; Olga Komarova, National Medical Research Center of Children's Health, Moscow, Russian Federation; Ida Safitri Laksono, Universitas Gadjah Mada, Yogyakarta, Indonesia; Rakesh Lodha, All India Institute of Medical Sciences, New Delhi, India; Julie Makani, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania; Hesham Ben Masaud, General Practice Council, Libyan Board of Medical Specialties, Tripoli, Libya; Refiloe Masekela, University of KwaZulu Natal, Durban, South Africa; Hilda Mujuru, University of Zimbabwe, Harare, Zimbabwe; Mary Paiva, National Department of Health, Buka General Hospital, Buka, Autonomous Region of Bougainville, Papua New Guinea; Abdulkarim Rasa'a, Faculty of Medicine Sana'a University, Sana'a, Yemen; Sergey Sargsyan, Arabkir Medical Centre, Yerevan State Medical University, Yerevan, Armenia; Dheeraj Shah, University College of Medical Sciences and GTB Hospital, New Delhi, India; Gezahegn Nekatibeb Techane, Debre Berhan University, Debre Birhan, Ethiopia; Leon Tshilolo, Université Officielle de Mbujimayi, Kinshasa, Democratic Republic of the Congo; and Dai Yaohua, Capital Institute of Paediatrics, Beijing, China. Many thanks to the co-chairs, Shams El Arifeen and Michael (Mike) English who chaired the Guideline Development Group meetings.

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WHO wishes to acknowledge the following external reviewers: Allan Da Caen, Stollery Children's Hospital University of Alberta, Edmonton, Alberta, Canada; Jayashree Muralidharan, Post Graduate Institute of Medical Education and Research, Chandigarh, India; Obiageli Nnodu, University of Abuja, Abuja, Nigeria; Haroon Saloojee, Witwatersrand University, Johannesburg, South Africa; Anju Seth, Lady Hardinge Medical College and Associated Kalawati Saran Children's Hospital, New Delhi, India; Varinder Singh, Lady Hardinge Medical College, New Delhi, India; and Ismail Ticklay, University of Zimbabwe, Harare, Zimbabwe.

Methodologists

WHO thanks the methodologists who guided the evidence reviewers and the Guideline Development Group discussions: Rebecca Morgan, McMaster University, Ontario, Canada, and Ife Babatunde, Case Western Reserve University School of Medicine, Cleveland, Ohio, United States of America.

Evidence synthesis team

WHO also acknowledges the following evidence synthesis and systematic review team from Amaris Consulting, UK Limited, London, United Kingdom of Great Britain and Northern Ireland: Robert Bagnall, Danielle Guy, Agathe Nevière, Gabriela Friedrich, Liga Bennetts, Omar Irfan and Isaac Odame.

WHO Steering Group members

We acknowledge the following WHO staff who participated as members of the guidelines Steering Group in the development process: Prerna Banati (Department of Sexual, Reproductive, Maternal, Child and Adolescent Health and Ageing), Jaden Bendabenda (Department of Nutrition and Food Safety), Bernadette Daelmans (Department of Sexual, Reproductive, Maternal, Child and Adolescent Health and Ageing), Tarun Dua (Department of Noncommunicable Diseases and Mental Health), Karen Edmond (Department of Sexual, Reproductive, Maternal, Child and Adolescent Health and Ageing), Bianca Hemmingsen (Department of Noncommunicable Diseases and Mental Health), Ivy Kasirye (Department for HIV, Tuberculosis, Hepatitis, Sexually Transmitted Infections), Peter Olumese (Malaria and Neglected Tropical Diseases), Martina Penazzato (Science for Health), Louise Puli (Department of Noncommunicable Diseases and Mental Health), Nigel Rollins (Department of Sexual, Reproductive, Maternal, Child and Adolescent Health and Ageing), Sarah Rylance (Department of Noncommunicable Diseases and Mental Health), Sabine Verkuijl (Department for HIV, Tuberculosis, Hepatitis, Sexually Transmitted Infections). Special thanks to WHO staff from regional and country offices: Jean-Marie Dangou, Teshome Desta and Roseline Doe, Regional Office for Africa; Pablo Duran, Regional Office for the Americas; Adela Mubasher and Khalid Siddeeg, Regional Office for the Eastern Mediterranean; Martin Will Weber, Regional Office for Europe; Deepti Agrawal and Neena Raina, Regional Office for South-East Asia and Daisuke Asai, Regional Office for the Western Pacific.

This work was coordinated by Wilson Were and Nuhu Yaqub, Department of Sexual, Reproductive, Maternal, Child and Adolescent Health and Ageing, WHO. Special thanks for administrative support goes to Laure Cartillier, Department of Sexual, Reproductive, Maternal, Child and Adolescent Health and Ageing, WHO. Lulu Muhe, independent consultant, Geneva, Switzerland, acted as rapporteur and writer.

Funding

The WHO guidelines for the management of sickle-cell disease in children and adolescents were funded by the Government of the Russian Federation through the maternal, newborn and paediatric quality of care improvement grant.

Abbreviations

ACS	acute chest syndrome
AMPS	aqueous multiphase system
CI	confidence interval
CZE	capillary zone electrophoresis
ECHO	echocardiogram
ERG	External Review Group
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GRC	Guidelines Review Committee
Hb	haemoglobin
HbA	normal adult haemoglobin
HbF	fetal haemoglobin
HbS	sickle-cell haemoglobin
Hib	*Haemophilus influenzae* type b
HPLC	high-performance liquid chromatography
IEF	isoelectric focusing
IPD	invasive pneumococcal disease
IM	intramuscular
IV	intravenous
LFIA	lateral flow immunoassay
LMIC	low- and middle-income country
NPV	negative predictive value
NRS	nonrandomized study
NSAID	non-steroidal anti-inflammatory drug
PaO_2	arterial partial pressure of oxygen
PCV	pneumococcal conjugate vaccine
PFT	pulmonary function testing
PICO	population, intervention, comparator and outcome
POCT	point-of-care test
PPV	positive predictive value
RCT	randomized controlled trial
RBC	red blood cell

RR	risk ratio
SCA	sickle-cell anaemia
SCD	sickle-cell disease
SCI	silent cerebral infarction
SD	standard deviation
SDG	Sustainable Development Goal
SpO_2	peripheral oxygen saturation
STOP	Stroke Prevention Trial in Sickle-Cell Anaemia
TCD	transcranial Doppler
TRV	tricuspid regurgitant velocity
USA	United States of America
VOC	vaso-occlusive crisis
WHO	World Health Organization

Glossary

Acute chest syndrome: A severe complication of sickle-cell disease characterized by chest pain, fever and difficulty breathing. It is often caused by infection or blockage of blood vessels in the lungs.

Capillary zone electrophoresis: A laboratory technique used to separate molecules based on their size and charge. It is commonly used to analyse haemoglobin variants in blood samples.

Echocardiogram: A non-invasive imaging test that uses ultrasound waves to create images of the heart. It helps assess heart function and detect abnormalities.

Haemoglobin: A protein in red blood cells that carries oxygen from the lungs to the rest of the body. Different types of haemoglobin include normal adult haemoglobin and sickle-cell haemoglobin.

Hydroxyurea: An oral antimetabolite medication used in sickle-cell disease, essential thrombocythemia, chronic myelogenous leukaemia, polycythaemia vera and cervical cancer. It is used to treat sickle-cell disease to decrease the number of attacks by increasing the production of fetal haemoglobin, which helps prevent red blood cells from sickling.

Intramuscular: A method of delivering medication by injecting it directly into a muscle.

Pulmonary function testing: A group of tests that measure how well the lungs are working, including how much air the lungs can hold and how quickly air can be exhaled.

Point-of-care tests: Diagnostic tests that are performed at or near the site of patient care, providing rapid results without the need for a central laboratory.

Sickle-cell anaemia: A severe form of sickle-cell disease where individuals inherit two sickle-cell genes, leading to the production of abnormal haemoglobin (HbS) that causes red blood cells to become rigid and sickle-shaped leading to various complications such as pain, anaemia and organ damage.

Sickle-cell disease: A group of inherited blood disorders that affect haemoglobin, which is the protein that carries oxygen in red blood cells.

Transcranial Doppler: An ultrasound technique used to measure blood flow velocities in the brain's blood vessels; this technique is often used to assess the risk of stroke in individuals with sickle-cell disease.

Tricuspid regurgitant velocity: A measurement obtained from an echocardiogram that estimates the pressure in the pulmonary artery, which is used to assess the presence of pulmonary hypertension.

Executive summary

Sickle-cell disease (SCD) is the most common inherited blood disorder worldwide, with the highest burden in low- and middle-income countries (LMICs). SCD leads to significant childhood morbidity and mortality, especially in regions where access to early diagnosis and comprehensive care is limited. This guideline provides the first evidence-based recommendations from the World Health Organization (WHO) for the diagnosis, prevention and management of SCD in children and adolescents (aged 0–19 years), with a focus on primary and secondary care and resource-limited settings.

The guideline is intended for policy-makers, clinicians and health workers responsible for the care of children and adolescents with SCD, particularly in LMICs. It addresses priority clinical topics, including diagnosis, infection prevention, disease-modifying therapy, pain management, acute complications, stroke prevention and screening for complications.

The recommendations in this guideline were developed through a rigorous process in line with WHO standards. This included conducting systematic reviews of the evidence to address key clinical questions and assessing the certainty of that evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The development process also involved careful consideration of the benefits and harms of interventions, as well as factors such as values, acceptability, feasibility, resource use and equity. A multidisciplinary Guideline Development Group with global representation reached consensus on the recommendations. The draft guideline then underwent external peer review and was approved by the WHO Guidelines Review Committee to ensure quality and credibility.

The guideline presents a total of 15 recommendations. Of these, 13 are conditional recommendations that require contextual adaptation due to low or very low certainty of evidence. Two recommendations are strong and prioritized for immediate action, even though the certainty of evidence is low. In addition, there are two areas where no recommendation could be made because of insufficient evidence, highlighting the need for further research and the importance of clinical judgement in these cases.

The recommendations are organized by key clinical topics relevant to the diagnosis, prevention and management of SCD in children and adolescents. Within each section, the recommendations are presented with supporting background, a summary of the evidence, justification for the recommendation and practical implementation considerations. This structure is designed to help users quickly locate guidance on specific clinical questions and understand the rationale, evidence base and practical steps for applying each recommendation in diverse health system settings.

Successful implementation of these recommendations requires careful adaptation to local contexts. Countries should tailor the guideline to their specific epidemiology, health system capacity and available resources, with particular attention to the feasibility and equity of conditional recommendations. Integration into national noncommunicable disease strategies, including PEN-Plus initiatives as well as child health programmes, essential medicines lists and treatment protocols, is essential to ensure comprehensive and coordinated care for children and adolescents with SCD.

Building the capacity of health workers is a key priority. This includes training on the use of diagnostic tools, administration of hydroxyurea, pain management protocols and transfusion safety. Ensuring a reliable supply chain is also critical; countries should work to guarantee the availability of hydroxyurea, penicillin, point-of-care tests (POCTs), and transfusion services and plan for iron chelation therapy where regular transfusion is recommended.Shared decision-making should be promoted by engaging caregivers and patients in understanding the benefits, risks and uncertainties of each intervention, especially where recommendations are conditional. Finally, robust monitoring and evaluation systems are needed. Countries should define indicators to track the uptake of recommendations, the availability of essential commodities, and adherence to decision-support tools, supporting continuous improvement and accountability.

The guideline also highlights several important research priorities. These include the need for studies on the long-term safety and optimal use of hydroxyurea, the effectiveness of interventions across different sickle-cell genotypes and settings, and the feasibility and cost-effectiveness of POCTs and transcranial Doppler screening in LMICs. Further research is needed to identify alternatives to chronic transfusion for stroke prevention and to better understand the impact of interventions on quality of life and neurocognitive outcomes for children and adolescents with SCD.

Implementation will require adaptation to local contexts, capacity-building and ongoing monitoring. By following these recommendations, countries can reduce morbidity and mortality, improve quality of life and advance health equity for children and adolescents living with SCD.

Summary of recommendations

Point-of-care test for diagnosis

Recommendation 1: In children and adolescents (aged 0–19 years) with suspected sickle-cell disease (SCD), the use of lateral flow immunoassay and micro-engineered haemoglobin electrophoresis point-of-care tests (POCTs) is suggested for diagnosis in settings where standard laboratory-based haemoglobin fractionation or DNA-based tests are not available.

Conditional recommendation, low certainty of evidence.

Remarks

- The primary objective of using POCTs is to facilitate early and timely diagnosis of SCD, enabling prompt initiation of treatment and care, particularly at the primary health care level.
- Following diagnosis, family screening is recommended to determine the haemoglobin genotype of both parents and siblings.
- In the immediate post-transfusion period, DNA-based testing is preferred. If not feasible, POCT should be delayed for at least 60 days post transfusion to reduce the risk of false-negative results due to the dilution by haemoglobin variants.
- Standard laboratory-based haemoglobin fractionation methods include haemoglobin electrophoresis, capillary zone electrophoresis, high-performance liquid chromatography and isoelectric focusing.

Antibiotic prophylaxis in children with SCD

Recommendation 2: In children aged less than 5 years with SCD, prophylactic penicillin (oral or intramuscular (IM)) is suggested to prevent pneumococcal infection, including in those who have received age-appropriate pneumococcal vaccination.

Conditional recommendation, low certainty of evidence.

Remarks

- Children with SCD aged less than 5 years are at increased risk of invasive pneumococcal disease. Prophylactic penicillin is recommended regardless of pneumococcal immunization status.
- Health care providers should engage families in shared decision-making regarding the choice between oral and IM penicillin, taking into account lifestyle, preferences and feasibility.
- For oral administration, dispersible tablets or liquid formulations are preferred to facilitate ease of use in young children.

- Adherence to oral prophylaxis may be suboptimal due to the need for daily administration and lack of provider oversight. IM administration ensures compliance but may be less acceptable to some families due to discomfort or logistic challenges.
- In children with a documented allergy to penicillin, erythromycin may be used as an alternative

Recommendation 3a: In children aged older than 5 years with SCD who have completed pneumococcal vaccination series and do not have additional risk factors, such as prior invasive pneumococcal infection or history of surgical splenectomy, prophylactic penicillin is not recommended.

Conditional recommendation, low certainty of evidence.

Recommendation 3b: In children aged older than 5 years with SCD who have not completed pneumococcal vaccination series, or who have a history of splenectomy or prior invasive pneumococcal infection, prophylactic penicillin is suggested, regardless of vaccination status.

Conditional recommendation, low certainty of evidence.

Remarks

- Children aged older than 5 years with SCD who are unvaccinated, who have undergone surgical splenectomy or who have a history of invasive pneumococcal infection are considered at high risk of serious infections and may benefit from continued penicillin prophylaxis.
- In contrast, children aged older than 5 years with fully developed immune systems and no additional risk factors are at lower risk of pneumococcal disease, and the benefit of continued prophylaxis is likely to be minimal.
- The potential benefit of extended penicillin use in older children should be carefully weighed up against the risk of promoting antimicrobial resistance, particularly in the context of global antimicrobial stewardship efforts.
- Where vaccination records are unavailable or uncertain, health care providers should use clinical judgement based on caregiver reports and local immunization practices to determine the child's likely vaccination status.
- Children with SCD should receive, and remain up to date with recommended vaccinations, including pneumococcal, Haemophilus influenzae type b and meningococcal vaccines along with booster or catch-up doses as appropriate.

No recommendation: WHO makes no recommendation on the use of antibiotics other than penicillin for pneumococcal prophylaxis in children and adolescents (aged 0–19 years) with SCD, due to insufficient evidence.

No recommendation due to insufficient evidence.

Remarks

- There is currently insufficient evidence to support an evidence-based recommendation regarding the use of alternative antibiotics to penicillin for pneumococcal prophylaxis in children and adolescents with SCD.
- Further research is needed to evaluate the efficacy and safety of non-penicillin antibiotic options in this population.

Hydroxyurea therapy

Recommendation 4: In children and adolescents (aged 9 months to 19 years) with sickle-cell anaemia (SCA), hydroxyurea therapy is recommended regardless of clinical severity.

Strong recommendation, low certainty of evidence.

Remarks

- Appropriate dosing and regular monitoring are essential to optimize the therapeutic benefits of hydroxyurea and minimize the risk of adverse events.
- Health care providers should offer clear, age-appropriate information to caregivers, children and adolescents to support informed decision-making and adherence.
- Acceptability and uptake of hydroxyurea can be enhanced through effective communication, counselling and advocacy by health care providers.
- Adolescents receiving hydroxyurea should be counselled on the need for contraception, as hydroxyurea is contraindicated during the first trimester of pregnancy due to potential embryo-fetal toxicity.

Pain management in SCD

Recommendation 5: In children and adolescents (aged 0–19 years) with SCD experiencing acute painful crises, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is suggested for initial pain management.

Conditional recommendation, very low certainty of evidence.

Remarks

- The Guideline Development Group (GDG) noted uncertainty regarding the generalizability of evidence from intravenous (IV) ketorolac to oral NSAIDs. However, oral NSAIDs were considered a more feasible and accessible option, particularly in primary care settings where IV formulations may not be available.
- When NSAIDs alone are insufficient for managing moderate to severe acute pain, a stepwise approach may be used: starting with paracetamol plus NSAIDs, followed by escalation to opioids if pain remains uncontrolled.
- Health care providers should conduct individualized risk assessments and clearly explain the potential benefits and harms of NSAIDs versus opioids to the children, adolescents and their caregivers to support informed decision-making.
- IV opioids may be a reasonable option when intravenous (IV) NSAIDs are unavailable or when rapid pain relief is prioritized. Patients who prioritize immediate pain relief over concerns about opioid-related side-effects may reasonably choose opioid analgesics for acute pain management.

Recommendation 6: In children and adolescents (aged 0–19 years) with SCD, the use of NSAIDs in combination with opioids is suggested for the management of moderate to severe acute pain, rather than opioids alone.

Conditional recommendation, low certainty of evidence.

Remarks

- The GDG acknowledged that in real-world settings, this recommendation may be implemented through a stepwise approach, initiating treatment with NSAIDs and escalating to combination therapy with opioids if pain is not adequately controlled.
- The decision to use NSAIDs in combination with opioids should be guided by the patient's baseline pain severity, individual preferences and a clear explanation of the potential benefits and harms of both NSAID and opioid therapies.
- Shared decision-making between health care providers, patients and caregivers is essential to ensure safe, effective and acceptable pain management.

Recommendation 7: In children and adolescents (aged 0–19 years) with SCD, the use of opioids alone is suggested for acute pain management rather than paracetamol plus opioids.

Conditional recommendation, very low certainty of evidence.

Remarks

- This recommendation is based on the evidence from studies using IV paracetamol in combination with opioids at the initiation of treatment, which did not demonstrate additional benefit compared to opioids alone.
- Health care providers should engage in shared decision-making with children, adolescents and their caregivers regarding the use of paracetamol versus opioids for managing pain at home, considering individual preferences, prior experiences and potential risks.

Recommendation 8: In children and adolescents (aged 0–19 years) with SCD, regular (chronic) blood transfusion with iron chelation therapy is suggested for the management of recurrent pain.

Conditional recommendation, very low certainty of evidence.

Remarks

- Regular blood transfusion should be offered through shared decision-making, with access to and adherence to regular monitoring of iron overload (e.g. serum ferritin or imaging) and appropriate iron chelation therapy.
- Patients and their families should be informed of the uncertainty regarding the benefits of regular transfusion relative to its potential burdens and risks, including iron overload and alloimmunization.
- For patients who prefer to avoid transfusion-related risks, NSAIDs and opioids may be considered as alternative options for managing recurrent pain.
- Given the cumulative exposure to blood products over the lifetime in individuals with SCD, hepatitis B immunization is recommended.
- Hydroxyurea therapy may be considered as an alternative to chronic blood transfusion for reducing recurrent pain, particularly in settings where transfusion or chelation therapy is limited or unavailable.

Management of acute chest syndrome (ACS)

Recommendation 9: In children and adolescents (aged 0–19 years) with SCD and a clinical diagnosis of ACS, the use of antibiotics in addition to standard therapeutic and supportive interventions is suggested.

Conditional recommendation, low certainty of evidence.

Remarks

- Empirical broad-spectrum antibiotic therapy should include a third-generation cephalosporin to cover common Gram-negative and Gram-positive organisms, along with a macrolide to target atypical bacteria such as Mycoplasma pneumoniae and Chlamydia pneumoniae.
- Where available, local bacterial prevalence and antimicrobial susceptibility patterns should guide the choice of specific antibiotics.

- In children, distinguishing ACS from pneumonia can be challenging due to overlapping clinical features. Infectious causes are more likely to be implicated in children than in adults.
- In cases of cephalosporin allergy, appropriate antibiotic alternatives should be considered based on local guidelines and susceptibility data.
- Standard therapeutic and supportive interventions for ACS include pain management, IV fluids, oxygen supplementation, blood transfusion or exchange transfusion, and respiratory support, as clinically indicated.

Recommendation 10: In children and adolescents (aged 0–19 years) with SCD and a clinical diagnosis of ACS, blood transfusion in combination with standard therapeutic interventions is suggested rather than standard therapeutic interventions alone.

Conditional recommendation, very low certainty of evidence.

Remarks

- Blood transfusion may improve oxygenation, which is a critical outcome in children with ACS, particularly in the presence of hypoxaemia and anaemia where a dose–response effect may be observed.
- The decision to initiate transfusion should be guided by the severity of ACS symptoms, including the presence of severe hypoxaemia, severe anaemia, stroke or clinical deterioration.
- In patients without hypoxaemia or a significant drop in haemoglobin, the potential risks of blood transfusion (e.g. alloimmunization, iron overload, transfusion reactions) may outweigh the uncertain benefits, and some patients may reasonably choose to decline transfusion.
- Shared decision-making with patients and caregivers is essential, taking into account clinical presentation, transfusion risks and patient values and preferences.

Stroke prevention and treatment in SCD

Recommendation 11: In children and adolescents (aged 0–19 years) with SCD and suspected acute symptomatic stroke, exchange transfusion is suggested rather than simple red blood cells (RBC) transfusion.

Conditional recommendation, very low certainty of evidence.

Remarks

- All children with suspected acute symptomatic stroke should receive prompt blood transfusion. Where exchange transfusion is not feasible or is delayed, simple RBC transfusion is an acceptable alternative.
- Simple transfusion should be administered with caution to avoid excessive increases in post-transfusion haemoglobin concentration, which may increase blood viscosity and worsen clinical outcomes.
- The choice between exchange and simple RBC transfusion should be guided by clinical urgency, local resource availability and the potential for improved outcomes with exchange transfusion, particularly in situations where rapid reduction of haemoglobin S is critical.

Recommendation 12: In children and adolescents (aged 0–19 years) with SCD at risk of recurrent stroke (e.g. history of stroke, haemoglobin S >30% and haemoglobin <9 g/dL), regular blood transfusion with iron chelation therapy is suggested rather than hydroxyurea therapy alone for secondary stroke prevention.

Conditional recommendation, very low certainty of evidence.

Remarks

- This recommendation assumes that all children and adolescents with SCA aged 9 months and older are already receiving hydroxyurea therapy as standard care. Regular blood transfusion and iron chelation are additional interventions specifically for secondary stroke prevention.
- In practice, children at risk of recurrent stroke may continue to receive hydroxyurea alongside regular blood transfusion and chelation therapy, depending on the clinical judgement and resource availability.
- The decision to initiate or continue transfusion therapy should be based on shared decision-making, considering the risks of iron overload, alloimmunization and the burden of chronic transfusion, balanced against the high risk of recurrent stroke.

Screening for complications in children with SCD

No recommendation: WHO makes no recommendation on the routine use of pulmonary function testing (PFT) in children and adolescents (aged 0–19 years) with SCD.

Remarks

- The GDG decided not to make a recommendation due to insufficient and indirect evidence. Available studies on PFTs in children and adolescents with SCD were not designed to address the specific PICO (population, intervention, comparator and outcome) question and did not demonstrate clear clinical benefit.
- There is currently no established link between abnormal PFT findings and actionable changes in clinical management that would improve outcomes or quality of life in this population.
- Performing PFTs in children aged less than 5 years is particularly challenging due to limited cooperation and test feasibility.
- Routine screening may carry unintended consequences, such as increased anxiety, unnecessary follow-up investigations or treatments without proven benefits.
- Although abnormal PFTs may help monitor pulmonary function over time, their role in routine screening for asymptomatic children with SCD remains unclear.

Recommendation 13: In children and adolescents (aged 0–19 years) with SCD who have no symptoms of pulmonary hypertension, routine echocardiogram screening to detect pulmonary hypertension is not suggested.

Conditional recommendation, low certainty of evidence.

Remarks

- Echocardiography may be appropriate in the presence of clinical signs or symptoms suggestive of pulmonary hypertension, such as persistent respiratory distress, recurrent hypoxaemia, chest pain at rest or with exertion, or other indicators of cardiopulmonary compromise.
- This recommendation reflects the limited evidence supporting the clinical utility of routine echocardiographic screening in asymptomatic individuals and the potential for unnecessary follow-up testing or interventions without proven benefit.

Recommendation 14: In children and adolescents (aged 2–16 years) with SCA and no prior abnormal transcranial Doppler (TCD) results, annual TCD ultrasound screening is recommended for primary prevention of stroke.

Strong recommendation, very low certainty of evidence.

Remarks

- Early identification of children at increased risk of stroke through TCD screening enables timely intervention and may help prevent serious complications such as stroke.
- In low-resource settings, standard ultrasound machines may be adapted for TCD screening using the appropriate probes, along with training of health care personnel at lower-level facilities.
- Patients and their families should be informed about the importance of stroke risk assessment and available options for primary stroke prevention, including regular TCD screening and follow-up care.

1. Introduction

Sickle-cell disease (SCD) is a red cell disorder in which normal adult haemoglobin (HbA) is replaced by sickle-cell haemoglobin (HbS). This is caused by a mutation in the β-globin gene (HbB), leading to substitution of valine for glutamic acid at position six of the β-globin subunit of the haemoglobin molecule. SCD refers to a group of disorders characterized by the presence of at least one βS allele and a second pathogenic β-globin gene variant that results in predominant production of HbS *(1)*. It is inherited as an autosomal recessive trait, and the most common types of SCD include homozygous SS, haemoglobin SC and sickle-cell β-thalassemia. Compound heterozygous forms result from co-inheritance with other HbB variants, including C (SCD-SC), the second most common, and β-thalassemia (SCD-Sβ^0 and SCD-Sβ^+). The genotypes SS and Sβ^0 are classified as sickle-cell anaemia (SCA) as these are associated with more severe clinical manifestations *(2, 3)*.

1.1 Epidemiology

SCD is the most common genetic disorder worldwide and is a growing global public health problem. In 2021, over half a million babies were born with SCD *(4)*. Approximately 90% of these births occur in low- and middle-income countries (LMICs) with the Democratic Republic of the Congo, India and Nigeria accounting for almost 50% of patients with SCD *(5, 6)*. Over the years, the prevalence of SCD has been increasing in both LMICs and high-income countries. A 2021 estimation of the global burden of disease showed that the number of people living with SCD globally increased by 41.4%, from 5.46 million in 2000 to 7.74 million in 2021, with 34 400 cause-specific all-age deaths globally in 2021. The total SCD mortality burden was nearly 11 times as much at 376 000 deaths *(4)*.

1.2 SCD presentation and management

SCD is a chronic disease characterized by haemolytic anaemia and endothelial dysfunction leading to vaso-occlusive crises (VOCs), acute chest syndrome (ACS), increased risk of stroke and a cumulative risk of multiorgan damage. Infants and children aged less than 5 years are at highest risk of morbidity and mortality from encapsulated bacterial infections due to functional asplenia. SCD is typically detected either by testing the amniotic fluid during pregnancy or through newborn screening shortly after birth *(7)*. In the absence of screening, most children with SCD die of sepsis, anaemia and other disease-related complications, including ACS, or are diagnosed late after infancy when they present with a fatal infection, severe anaemia or acute splenic sequestration and other complications.

There have been many advances in care leading to significant reduction in morbidity, mortality and improved quality of life for individuals living with SCD. The improvement in survival is mainly attributable to universal newborn screening, early initiation of antimicrobial prophylaxis and immunization, the use of hydroxyurea, regular blood transfusions and the use of transcranial Doppler (TCD) ultrasound to monitor the risk of stroke *(5, 6, 8-10)*. Unfortunately, while these are simple and relatively inexpensive evidence-based interventions, they are more readily available in high-income settings that represent <5% of the global SCD population *(11-13)*. In LMICs, particularly in sub-Saharan Africa, 50–90% of children with SCD still die before the age of 5 years because these interventions are not currently provided as a standard of care or are mostly inaccessible to patients *(14)*.

1.3 Purpose and rationale

In 2006, the World Health Assembly passed a resolution recognizing SCD as a public health priority and called on countries to tackle the disease *(15)*. The resolution called on WHO to provide normative guidance and practical care models, on the prevention and management of SCA. This resolution was also adopted by the United Nations in 2009 *(16)*. Addressing SCD would significantly contribute to achieving the Sustainable Development Goal (SDG) targets for maternal mortality (SDG 3.1), neonatal mortality and mortality of children aged under 5 years old (SDG 3.2) and the reduction of mortality due to noncommunicable diseases (NCDs) (SDG 3.4) *(4, 14)*. As child mortality declines, there is an increasing recognition of the epidemiological transition and the importance of NCDs as major causes of mortality in children and adolescents *(17)*. In 2021, in children aged less than 5 years, there were 81 100 deaths due to SCD *(4)*.

To date, there is no WHO normative guidance on the clinical management of SCD in children, and neither the *Pocket book of hospital care for children (18)* nor the *Integrated management of childhood illness (IMCI) chart booklet* address SCD *(19)*. Yet care for patients with SCD is often the responsibility of primary health care workers, family and non-specialized physicians. For example, although 23 countries in the WHO African Region are defined as high burden for SCD, in 2020, only eight countries had developed an SCD strategy *(20)*. This guideline provides evidence-based recommendations for health professionals and patients on the management of SCD, taking into consideration patient preferences and values, and highlighting gaps for further clinical research where needed.

1.4 Scope and target audience

This guideline focuses on selected topics related to the diagnosis and management of children and adolescents (aged 0–19 years) with SCD. It does not encompass all aspects of SCD management but only priority clinical aspects for primary and secondary care levels (see Annex 1). The guideline specifically addresses the following:

- using point-of-care tests (POCTs) for diagnosis;
- antibiotic prophylaxis against pneumococcal infection;
- using hydroxyurea therapy in patients with SCD;
- using non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and opioids for pain control and management;
- using antibiotics and blood transfusion for the management of ACS;
- prevention and management of stroke; and
- screening for SCD complications.

The target audience are policy-makers and health care professionals working across diverse settings and with variable availability of resources, particularly in LMICs and regions with a high SCD burden.

2. Process and methods

The guidelines for the management of SCD in children and adolescents were developed in accordance with the principles and procedures outlined in the *WHO handbook for guideline development (21)*. The guideline development process followed WHO's standard steps, which include: (i) defining the general scope of the recommendations; (ii) identifying contributors and establishing the Guideline Development Group (GDG); (iii) formulating key questions and outcomes using the population, intervention, comparator and outcome (PICO) format; (iv) conducting systematic evidence reviews; (v) assessing the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach; (vi) formulating recommendations and drafting of the guideline narrative; (vii) reviewing and approving the recommendations through the GDG; (viii) conducting external peer review; (ix) submitting the guideline for review and approval by WHO's Guidelines Review Committee; and (x) finalizing and disseminating the final recommendations.

2.1 Contributors

A diverse group of contributors participated in the guideline development process, including clinical experts, methodologists, health system specialists and representatives from WHO headquarters and its regional and country offices. All contributors were selected based on their expertise and experience, and their roles were clearly defined in line with WHO policies to ensure effectiveness, transparency and minimize bias.

The WHO Steering Group comprised members from relevant technical units at WHO headquarters and WHO's regional and country offices. The WHO Steering Group provided technical oversight, coordinated the process and supported project management. This Group also established the general scope of the guideline, drafted potential key questions and identified and selected the GDG members.

The GDG included members from all WHO regions and a range of professional backgrounds. Their expertise covered the clinical management of SCD, as well as health systems, programme implementation and patient care. The GDG was supported by a guideline methodologist, who ensured methodological rigour throughout the process.

Systematic review teams were commissioned to synthesize the evidence for each key question. An External Review Group, composed of technical and implementation experts, reviewed the final draft of the guideline and provided feedback on content and presentation.

2.2 Management of conflict of interest

In accordance with the *WHO handbook for guideline development (21),* all individuals involved in the guideline development process, including members of the GDG, external reviewers and contributors, were required to disclose any potential conflicts of interest. These disclosures were reviewed by WHO staff and assessed for relevance and severity. Where a conflict of interest was identified, appropriate measures were taken to manage it, including exclusion from specific discussions or decisions, or full recusal from participation. The objective was to ensure transparency, maintain the integrity of the guideline development process and safeguard against undue influence. All conflict-of-interest declarations and management decisions were documented and are available upon request. Only individuals with no significant conflicts of interest were formally invited to join the GDG or External Review Group. Further details are provided in Annex 2.

2.3 Evidence retrieval and synthesis

At the initial two virtual GDG meetings, the GDG established the scope of the guideline; the key questions, using the PICO format; and identified key outcomes. Systematic reviews were commissioned to address each of the prioritized PICO questions (see Annex 1). These reviews adhered to Cochrane methods and standards and were conducted by independent review teams *(22)*. The GRADE approach was used to assess the certainty of evidence for each critical and important outcome *(23)*. Detailed methods are described in the respective systematic reviews (Web Annex *(24)*).

2.4 Evidence assessment

The protocols for the systematic reviews were developed by the research teams, and subsequently reviewed by the coordinating team, methodologists and the GDG co-chairs before the literature retrieval. This review ensured adherence to the best practice methods for systematic reviews. The protocols were evaluated based on their search approach, their thoroughness and clear definitions of the PICO process used to guide the eligibility criteria for literature retrieval and the methods used for assessing the risk of bias in the included studies. Authors were also encouraged to prospectively register their review titles on the International Prospective Register of Systematic Reviews (PROSPERO).

The reviewers systematically searched EMBASE, PubMed, Cochrane libraries and registries, including institutional databases and conference proceedings where relevant, without language restrictions. The included studies were extracted using a pre-defined form and verified. The final systematic review reports underwent quality assessment, with an emphasis on the eligibility of the included studies, the risk of bias assessment for these studies and their results. The GRADE tool was used to assess the certainty of evidence for the included outcomes and the conclusions drawn. Evidence profiles were created using GRADEpro, and the evidence-to-decision framework was pre-populated with the available evidence.

The GRADE approach was used to appraise the quality of quantitative evidence for all critical outcomes identified in the PICO questions. For each outcome within every key question, a GRADE profile was created, classifying the certainty of the evidence into four categories: high, moderate, low or very low, as defined in the *WHO handbook for guideline development* (Table 1) *(21).*

Table 1. Using the GRADE approach to appraise the quality of quantitative evidence

Certainty	Interpretation
High	High confidence that the true effect lies close to that of the estimate of the effect
Moderate	Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	Little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

Source: Guyatt et al. *(23)*.

This classification was determined based on the quality of the evidence, including the types and sizes of the studies conducted. Initially, randomized controlled trials (RCTs) are considered to provide high-quality evidence, whereas nonrandomized trials and observational studies typically start as low-quality evidence. This initial quality rating for both RCTs and nonrandomized trials was then adjusted after assessing for factors such as study design limitations (risk of bias), inconsistency, imprecision, indirectness and publication bias, and, in the case of observational studies, the evidence rating could be upgraded for studies where there was a significant magnitude of effect, provided there were no overriding limitations necessitating a downgrade.

The systematic review teams, supported by the guideline methodologist, retrieved, appraised and synthesized evidence, following the guidance in the *WHO handbook for guideline development (21)*. Wherever feasible, evidence was presented in the form of a meta-analysis. In situations where a meta-analysis was not possible, a narrative synthesis of the findings was conducted. Reports for all systematic reviews, including GRADE evidence profiles, were distributed to GDG members prior to GDG meetings. Unpublished systematic review reports can be accessed in the Web Annex *(24)*.

2.5 Formulation of recommendations

The GDG meet virtually and in person between July 2023 and February 2024 to review the evidence and formulate recommendations. The meetings were chaired by a GDG member and facilitated by the guideline methodologist. The GDG used an explicit evidence-to-decision framework to guide discussions and ensure transparency in decision-making.

Recommendations were based on a balance of benefits and harms, the certainty of evidence, values and preferences, acceptability, feasibility, resource use and equity considerations. Each recommendation was classified as either strong or conditional, with:

- a **strong recommendation** indicating high confidence that the desirable effects outweigh the undesirable effects; and
- a **conditional recommendation** reflecting less certainty, acknowledging that the balance of desirable effects may vary on context or stakeholder values. The choices of individuals and policy or decision-makers will vary according to the relative values placed on the outcomes, acceptability, resources and other considerations.
- Consensus was the primary method for decision-making. All GDG members present had to agree on the final wording and the strength of each recommendation. If consensus could not be reached, a vote was planned as the fallback approach. Only GDG members participated in the decision-making process, although WHO staff, the methodologist and observers contributed to discussions.
- The GDG also identified research gaps during the formulation process. These reflect the uncertainties in the evidence base and highlight areas where further research could improve future guideline development and clinical decision-making. These research gaps are not prioritized or exhaustive but are intended to inform future research agendas.
- Following the GDG meeting, the guideline writer drafted the narrative sections, which were reviewed and approved by the GDG, and then submitted for external peer review by the External Review Group. After incorporating the feedback, the final recommendations were reviewed and approved by WHO's Guidelines Review Committee and prepared for publication and dissemination.

3. Recommendations

3.1 POCTs for the diagnosis of SCD

3.1.1 Background

SCD is typically detected either during pregnancy, through testing the amniotic fluid, or through screening shortly after birth. Early diagnosis, with subsequent provision of preventive measures and comprehensive care, is highly effective in reducing morbidity and early mortality, and improving quality of life *(25-27)*. In the absence of antenatal or newborn screening, SCD is typically diagnosed around 6–12 months following an initial presentation of dactylitis, a serious infection, or acute splenic sequestration as levels of fetal haemoglobin (HbF) decline and HbS begins to predominate.

Standard diagnosis of SCD is laborious and often requires specialized laboratory equipment and skilled technicians. It uses a combination of biochemical and molecular tests in the detection and confirmation of the diagnosis of SCD *(28)*. The methods routinely used in identifying, separating and quantifying the normal and variant haemoglobin are based on the fractionation of haemoglobin molecules *(29)*. These include classical electrophoresis (cellulose acetate and citrate agar), isoelectric focusing (IEF), high-performance liquid chromatography (HPLC), capillary zone electrophoresis (CZE) or polymerase chain reaction (PCR)-based DNA analysis *(7)*. These are expensive and need to be done in specialized laboratories by highly skilled personnel, although they have high sensitivity and specificity, and are currently used as reference standards.

Use of these diagnostic tests remains a challenge in many low-resource settings in part due to inadequate financial, laboratory and technical resources to carry out these diagnostics. However, new diagnostic techniques have emerged including paper-based haemoglobin solubility assays, lateral flow immunoassays (LFIAs), micro-engineering haemoglobin electrophoresis, density-based separation techniques and smartphone-based image processing techniques *(7, 29-31)*. The paper-based haemoglobin solubility test builds on the physiological principle that deoxy-HbS becomes insoluble in high concentrations of a phosphate buffer *(29, 30)*. The LFIA is based on polyclonal and monoclonal antibody–antigen complexes, formed between commercial antibodies and haemoglobin *(29, 32, 33)*. The micro-engineering haemoglobin electrophoresis assay is a miniaturized version of cellulose acetate electrophoresis, comprised of an electric field applied using internal electrodes, which causes separation of haemoglobin in bands, based on a charge within an alkaline medium *(29, 30)*. Density-based separation uses the tendency of sickled red blood cells (RBCs) to dehydrate, which increases the density of the cell and allows for the precipitation of the RBCs to the bottom of the tubes according to density *(30, 34)*. Lastly, a smartphone-based application with a sickle-cell tester takes advantage of the increased density and lower levitation of the sickled RBCs, and uses an optical light-emitting diode and the phone camera to capture images *(29)*.

It is important that these tests are accurate with high sensitivity and specificity in the hands of end-users. In line with WHO's ASSURED criteria, an ideal POCT in resource-limited settings should be rapid (fast turnaround to provide treatment and education at the same visit), simple to use (requiring few facilities, equipment or training), low cost, easily interpretable and stable when transported and stored under extreme temperature and humidity conditions *(35)*. The recent advent and commercial availability of inexpensive, simple, accurate and practical POCTs for SCD may directly address the challenges in high-prevalence and low-resource settings *(29)*.

Recommendation 1:

In children and adolescents (aged 0–19 years) with suspected SCD, the use of lateral flow immunoassay and micro-engineered haemoglobin electrophoresis POCTs is suggested for diagnosis in settings where standard laboratory-based haemoglobin fractionation or DNA-based tests are not available.

Conditional recommendation, low certainty of evidence.

Remarks

- The primary objective of using POCTs is to facilitate early and timely diagnosis of SCD, enabling prompt initiation of treatment and care, particularly at the primary health care level.
- Following diagnosis, family screening is recommended to determine the haemoglobin genotype of both parents and siblings.
- In the immediate post-transfusion period, DNA-based testing is preferred. If not feasible, POCT should be delayed for at least 60 days post transfusion to reduce the risk of false-negative results due to the dilution by haemoglobin variants.
- Standard laboratory-based haemoglobin fractionation methods include haemoglobin electrophoresis, CZE, HPLC and IEF.

3.1.2 Justification

SCD is a life-threatening condition of childhood with under-5 mortality rates estimated between 50–90% in LMICs *(2)*, largely due to delayed diagnosis and lack of timely access to preventive interventions such as parental education, penicillin prophylaxis and disease-modifying therapies. Most affected infants die from preventable complications within the first few years of life.

POCTs, including LFIAs and micro-engineered haemoglobin electrophoresis, have demonstrated high sensitivity and specificity based on predefined thresholds, with moderate to high certainty of evidence for diagnostic accuracy for both neonates, children and adolescents. The GDG agreed that the benefits of using the POCTs for diagnosing SCD are substantial, particularly due to their accuracy and rapid turnaround time at the point of care.

Compared to standard laboratory-based diagnostics, POCTs are more affordable, easier to use and require fewer resources, making them more accessible across various levels of the health system. The GDG concluded that the use of POCTs would enhance early diagnosis, facilitate timely initiation of care and improve health equity, especially in resource-limited settings.

3.1.3 Summary of evidence

The systematic review identified 32 cross-sectional studies that met the search criteria, and 24 of the studies included sites in LMICs *(36)*. All studies reported sensitivity and specificity, of which 11 also reported positive predictive values (PPVs) and negative predictive values. A total of 19 761 participants were recruited, of which 11 studies included neonates and infants, 12 included only children, 11 included children and adolescents, nine studies included a few adults, and five studies did not report the age range. Studies typically did not only include populations suspected of having SCD, but also the general population (n = 17). POCTs typically tested for SCD-SS, SCD-SC, sickle-cell trait and normal blood cells. A wide range of types of POCTs were used in the studies, with LFIAs being the most commonly assessed in 21 studies, of which 10 studies assessed HemoTypeSC alone, eight assessed SickleSCAN alone, two assessed HemoTypeSC and Sicke SCAN (compared to IEF (n = 1) or each other (n = 1)), and one assessed an unnamed lateral flow immunoassay. Four studies assessed micro-engineered haemoglobin electrophoresis tests, three assessed aqueous multiphase system-based (AMPS) tests, two assessed paper-based SCD assays and one study each assessed visual, colour-based assay tests, nucleic acid tests and the end-tidal carbon monoxide monitor. The reference standard, or gold standard, used as a comparator included: haemoglobin electrophoresis (seven studies); IEF (six studies); and HPLC (19 studies); and a combination of multiple reference tests was used in 12 studies.

The studies showed that a number of POCTs, particularly LFIAs, have been assessed extensively for diagnostic accuracy and demonstrated high sensitivity and specificity in general, although there was wide variation in the individual sensitivity (67–100%) and specificity (60–100%) estimates across all the tests *(36)*. The low sensitivity and specificity estimates were typically found in tests that used AMPS techniques. Some of the POCTs that included newborn and infant populations showed high sensitivity and specificity even in these populations. When comparing all the POCTs, LFIAs and micro-engineered haemoglobin electrophoresis were more widely studied and had the highest diagnostic accuracy with minimal differences between these tests for both sensitivity and specificity.

Accuracy of POCTs

The sensitivity, specificity, PPV and NPV for SickleSCAN were all 100% in all studies for populations of older children, where it was possible to separate out newborn populations *(36)*. For HemoTypeSC, sensitivity was high except in one study where it was 85.7% due to one false-negative result in a sample of eight, and a low PPV of 56.3% due to several discordant results at one site. When results from this site were excluded, the PPV was 93.8%. However, the certainty of evidence for HemoTypeSC was rated as very low for the detection of true positives and low for the detection of true negatives because of a serious risk of bias and very serious imprecision or serious imprecision of the studies, respectively. Similarly, in neonates and infants, the certainty of evidence for SickleSCAN was rated as very low for the detection of true positives and moderate for the detection of true negatives for the same reasons *(36)*.

Gazelle-Multispectoral had 100% sensitivity, specificity, PPV and NPV for SCD-SS in neonates *(36)*. The certainty of evidence for Gazelle-Multispectral was low to moderate, due to limited samples from a single study because of imprecision. In the older and broader population, the certainty of evidence for all outcomes for HemoTypeSC, SickleSCAN and Gazelle-Multispectral was low or moderate because of inconsistencies.

The GDG recognized that the threshold for false negatives should be less than or equal to the threshold for false positives, and that a threshold of 5 per 1000 tests for false positives and a threshold of less than 5 per 1000 for false negatives could be tolerated. Based on these thresholds and the sensitivity and specificity, the certainty of evidence for accuracy was rated as moderate to high for neonates and older populations for the three POCTs: HemoTypeSC, SickleSCAN and Gazelle-Multispectral (Table 2).

Table 2 Summary of the certainty of evidence for POCT accuracy

Age group	HemoTypeSC	SickleSCAN	Gazelle-Multispectral
Neonates and infants	Accurate	Very accurate	Very accurate
Children	Very accurate	Accurate	Very accurate

Benefits and desirable effects

The potential benefits of using the POCTs for diagnosis of SCD in children and adolescents are large because of the accuracy and direct benefits of faster turnaround times at the point of care. A positive POCT result ensures that comprehensive SCD management is immediately initiated. Early diagnosis and provision of interventions, such as penicillin prophylaxis therapy, vaccination, parental education and hydroxyurea, will improve quality of life and reduce preventable SCD morbidity and mortality. In addition, genetic counselling can be provided to the patients and families. Patients with negative tests (true and false) will benefit from genetic counselling, clinical management and retesting, or the use of a confirmatory test for those who continue to have symptoms.

Harms and undesirable effects

The systematic review did not identify adverse events. However, the GDG perceived minimal harms due to pain from drawing blood, and anxiety for patients and family members. In the case of false positives, an incorrect diagnosis of SCD will mean starting on penicillin prophylaxis that might be of low harm for a child without SCD. Since hydroxyurea is started from the age of 9 months, it allows for the possibility of the diagnosis being corrected. A false negative may deny a child initiation of comprehensive SCD care, which leaves them vulnerable to complications; however, if symptomatic, they may be picked up upon retesting. In some cases, post blood transfusion, the POCT result could be a false negative because of the transfusion. In this situation, when SCD is suspected, the ideal test would be a quantitative test such as HPLC or haemoglobin electrophoresis.

Other considerations

Preferences, values and acceptability: The GDG felt that there is no variability between patients or caregivers on how one test over the other is valued. The GDG felt that the providers and patients, or their caregivers, will value POCTs over laboratory tests because of the quick turnaround and low cost. Earlier diagnosis using POCTs is most likely to be acceptable to key stakeholders (e.g. patients, caregivers, clinicians, pharmacists, governments) because of the earlier interventions that it makes possible.

Resources required: No studies evaluated the cost of POCTs compared to laboratory tests; however, overall, the POCTs are less costly compared to laboratory tests because of the lower resource requirements. The GDG noted that the cost varies with the estimated cost of available POCTs, varying from US$ 2.00 to US$ 4.50, except for the Gazelle-Multispectral test which requires an initial equipment cost (currently about US$ 15 000) *(37-39)*. In comparison, the cost per test done in the lab is US$ 6–10 in addition to the equipment and expertise required; hence, POCTs allow for moderate savings. No studies assessed the cost-effectiveness of each POCT versus laboratory testing.

Equity: The GDG considered the potential of the POCTs to increase equity because of the faster diagnosis of SCD in LMICs leading to early management decisions and decreasing mortality. The GDG members noted that the Gazelle equipment and kit is being simplified and modified and that the newer versions would not require as much infrastructure. GDG members also noted that Gazelle-Multispectral is the only POCT that can quantify the type of haemoglobin, which would be beneficial in monitoring therapy.

Feasibility: The GDG panel noted that this recommendation is feasible to implement because POCTs provide rapid results at the point of care and require limited laboratory expertise and facilities. However, their implementation will require the health system taking into consideration the following: capacity-building in terms of skills of health care providers and making the kits available at the primary health care level, education of health care workers, including specialists and making the tests more affordable and accessible particularly in rural areas for lower income and vulnerable populations. The Gazelle-Multispectral test is the only one of the three tests that can quantify the result.

3.1.4 Research gaps

Further research is needed to inform the optimal use, implementation and scale up of point-of-care testing for SCD, particularly in LMICs. The following areas have been identified as priorities:

- cost-effectiveness and feasibility studies comparing POCTs with standard laboratory diagnostic methods to determine whether the broader implementation of POCTs is justified, particularly in limited resource settings;
- comparative studies of multiple POCT platforms across diverse clinical and geographical contexts to assess the diagnostic accuracy, usability and operational performance;
- long-term population-level impact assessments of POCT introduction in LMICs, including effects on early diagnosis, treatment initiation and health outcomes;
- implementation research to evaluate effective models for scaling up the use of POCTs, including strategies for training and upskilling health care providers at different levels of the health system; and
- research to generate evidence on contextual factors, including on acceptability, feasibility, resource use, cost-effectiveness, equity and stakeholder values to support informed policy and programmatic decisions.

3.2 Antibiotic prophylaxis in children with SCD

3.2.1 Background

Infants and young children with homozygous SCD are particularly susceptible to bacterial infections *(40)*. This is partly due to impairment of the immune system resulting from splenic dysfunction, and abnormalities in the complement system, immunoglobulins, leukocyte function and cell-mediated immunity *(41, 42)*. This leads to an increased risk of encapsulated bacterial infections, particularly pneumococcus, but also *Haemophilus influenzae*, *Staphylococcus aureus*, *Escherichia coli* septicaemias *(42, 43)* and *Salmonella*. Pneumococcal infection accounts for 50% to 70% of overwhelming sepsis with high mortality rates ranging from 35% to 50% *(44)*. Before the advent of penicillin prophylaxis, there was a high case fatality rate among children with SCD with *Streptococcus pneumoniae* infections often progressing quickly to death in less than 24 hours from onset *(10, 45)*. Prophylactic penicillin has been shown to significantly reduce the risk of pneumococcal infection in children with homozygous SCD, with minimal adverse reactions *(46)*.

In addition, the advent of the pneumococcal conjugate vaccine (PCV) and the *Haemophilus influenzae* type b (Hib) vaccine, both administered during early infancy, has markedly contributed to the reduced risk of invasive bacterial infections *(47-50)*. However, some strains of pneumococcus that are not currently covered by the available vaccines are emerging *(48, 51, 52)*. In addition, other bacterial infections such as *Salmonella*, *S. aureus* and *E. coli* also commonly cause infections in patients with SCD, especially in tropical settings *(44, 53)*. There are no specific vaccines against some of these bacterial infections, so vaccination availability is limited.

In children aged less than 5 years who have received pneumococcal vaccination, studies have shown that penicillin prophylaxis reduces pneumococcal infection and mortality *(14, 45)*. However, the extent to which these benefits continue in children with SCD aged older than 5 years, when a child's immune system is typically sufficiently developed to avoid more severe infections, is less clear *(54-56)*. Currently, there is no consensus on the termination or continuation of penicillin prophylaxis for a longer period beyond the age of 5 years *(57, 58)*. Based on findings from the PROPS II trial, some guidelines recommend discontinuation, except in patients with surgical asplenia or prior invasive pneumococcal infection *(54, 57)*. Conversely, some guidelines recommend lifelong penicillin prophylaxis in high-risk patients, such as those with surgical asplenia, prior invasive pneumococcal infection and those aged less than 16 years, as well as for any child with hyposplenia or asplenia *(57)*. Nevertheless, there are challenges with ensuring patient adherence, the potential for penicillin allergy and antimicrobial resistance *(59-63)*. In view of these uncertainties, there was a need to evaluate the evidence on penicillin prophylaxis in children with SCD.

3.2.2 Antibiotic prophylaxis for children aged <5 years old with SCD who have

Recommendation 2:

In children aged less than 5 years with SCD, prophylactic penicillin (oral or intramuscular (IM)) is suggested to prevent pneumococcal infection, including in those who have received age-appropriate pneumococcal vaccination.

Conditional recommendation, low certainty of evidence.

Remarks

- Children with SCD aged less than 5 years are at increased risk of invasive pneumococcal disease. Prophylactic penicillin is recommended regardless of pneumococcal immunization status.
- Health care providers should engage families in shared decision-making regarding the choice between oral and IM penicillin, taking into account lifestyle, preferences and feasibility.
- For oral administration, dispersible tablets or liquid formulations are preferred to facilitate ease of use in young children.
- Adherence to oral prophylaxis may be suboptimal due to the need for daily administration and lack of provider oversight. IM administration ensures compliance but may be less acceptable to some families due to discomfort or logistic challenges.
- In children with a documented allergy to penicillin, erythromycin may be used as an alternative.

Justification

Children with SCD are at significantly increased risk of life-threatening infections caused by encapsulated bacteria, particularly pneumococcus, but also *H. influenzae*, *S. aureus*, *E. coli* septicaemias and *Salmonella*. Prior to the introduction of penicillin prophylaxis, the case fatality rate from pneumococcal sepsis or meningitis in children with SCD was high, with many deaths occurring within 24 hours of symptom onset.

The GDG determined that penicillin prophylaxis substantially reduces infection-related morbidity and mortality in young children with SCD. It is considered affordable, acceptable and feasible to implement, including in LMICs. Although the available evidence does not specifically include children who received PCV, the GDG judged that the relative benefit of penicillin prophylaxis remains relevant. Breakthrough infections can still occur in vaccinated children, particularly in early childhood when vaccine-induced immunity may be incomplete.

Furthermore, penicillin prophylaxis may offer protection against other bacterial pathogens not covered by current vaccines, such as *S. aureus, E. coli* and *Salmonella* species. For these reasons, the GDG concluded that penicillin prophylaxis remains a valuable intervention for children aged less than 5 years with SCD, regardless of their pneumococcal vaccination status.

Summary of evidence

The systematic review identified two clinical trials covering 457 children aged less than 5 years with homozygous SCD (SCD-SS) assessing the role of penicillin in preventing *S. pneumoniae*-related infections. The two RCTs were the Pneumococcal Prevention Study in Jamaica and the PROPS study in the United States of America (USA) *(64, 65)*. Both studies excluded those with a history of pneumococcal infection or splenectomy, or children receiving long-term antibiotics, transfusion or who had penicillin allergy. The Jamaica study assessed the impact of the 14-valent vaccine versus the Hib vaccine and monthly IM penicillin versus no penicillin *(64)*. The USA PROPS study was a randomized, double-blind, placebo-controlled multicentre trial to test whether oral penicillin would reduce incidence of documented septicaemia due to *S. pneumoniae (65)*.

In the Jamaica study, there was an overall incidence of six pneumococcal isolations in 99 participants (280 patient-years at risk) in the placebo groups, compared to seven events in 143 participants (400 patient-years at risk) in the penicillin groups (risk ratio (RR): 0.82; 95% confidence interval (CI): 0.28–2.36) *(64)*. No pneumococcal events occurred in children receiving penicillin prophylaxis, and no deaths occurred after the initiation of treatment. In the PROPS trial, there were two cases of confirmed pneumococcal infection among 105 participants in the penicillin group compared to 13 cases of infection among 110 participants in the placebo group (RR: 0.18; 95% CI: 0.04–0.77) *(65)*. In the meta-analysis, invasive pneumococcal pneumonia was found in two out of 202 children in the penicillin arm and in 14 out of 172 children in the no penicillin arm (RR: 0.13; 95% CI: 0.03–0.57). There were no deaths in the Jamaica study or in the penicillin group of the PROPS study, but there were three deaths in the control group. In both studies, no serious adverse events were reported, and in the PROPS trial the tablets were well-tolerated.

Overall, both studies suggest that penicillin prophylaxis in children aged less than 5 years who have been vaccinated against pneumococcal infection could result in a lower incidence of infections such as septicaemia (RR: 0.17; 95% CI: 0.04–0.64). The findings also suggest that prophylactic penicillin could reduce mortality in these populations. The certainty of the evidence across the key outcomes was judged to be low. This was primarily driven by the risk of bias reported for these trials and imprecision, given the low number of event rates reported for the outcomes observed.

Benefits and desirable effects

The GDG judged the desirable effects as moderate for penicillin prophylaxis in reducing the incidence of pneumococcal infections in children with SCD aged less than 5 years. This was driven by the reduction of invasive pneumococcal infection rates to 68 per 1000 patients by penicillin prophylaxis intervention compared to no antibiotics. There was a lower impact on mortality shown by the PROPS study, with a reduction of 23 deaths among children who were on penicillin prophylaxis. However, concerns were raised about the indirectness of the evidence because both trials were conducted before the era of PCV vaccination in children. However, the GDG recognized that even with PCV vaccination only 50% of children may be protected due to other pneumococcal serotypes not covered by the current 13-valent vaccine *(48)*. In addition, consideration was given to other possible bacterial infections not covered by the current routine vaccination.

Harms and undesirable effects

The GDG judged the undesirable effects as trivial for oral penicillin and small for IM penicillin. This was driven by the absence of serious adverse events reported in both studies, and the known rare possibility of anaphylactic reactions that can occur with IM administration. Penicillin is also used to treat a range of other bacterial infections, and adverse events are typically reported to be low. Nevertheless, penicillin V and G have been known to have adverse effects, including nausea, vomiting, diarrhoea, rash, abdominal pain and urticaria. In addition, IM penicillin G can have other adverse reactions, including muscle spasms, fever, chills, muscle pain, headache, tachycardia, flushing, tachypnoea and hypotension *(61)*.

Other considerations

Preferences, values and acceptability: Patients and caregivers value the prevention of pneumococcal infections, crises and hospitalizations that could result from penicillin prophylaxis. Caregivers, if adequately counselled, will possibly feel that their children are protected from infection with the intervention. However, due to the poor taste of the medication as well as hypersensitivity, vomiting and nausea, patients may not be compliant to the treatment. One study found that among 421 SCD patients taking penicillin V, adherence ranged from 30% to 68% depending on the caregiver *(62, 66)*. The discomfort from the IM injections also has the potential to affect adherence. However, one study found high compliance (88.5%) with IM penicillin prophylaxis, and a lower incidence rate of invasive pneumococcal disease, reflecting the difference with the route of administration *(61)*. Given these observations, the GDG judged that there is possible important uncertainty or variability in how children, adolescents and caregivers may value the main outcomes, which may influence acceptability across different settings. The GDG also noted that the use of concomitant hydroxyurea or other management medications could influence treatment adherence.

Equity: The GDG judged that the recommendation probably has no impact on equity because of the wide availability of penicillin, and that oral penicillin can easily be provided at all levels of the health system, even in LMICs, to ensure access for most of the population, using similar approaches to the global malaria programme.

Resources required: There was not enough evidence to assess cost and cost-effectiveness, but the GDG used other studies to decide on the cost-effectiveness of the intervention as probably favouring penicillin prophylaxis *(67-69)*. This was because of the impact of prophylaxis in preventing invasive pneumococcal disease, which could lead to reductions in the cost of hospitalizations *(68)*. Penicillin prophylaxis, which costs US$ 647.32 annually in children with SCD aged less than 5 years, is cost-effective compared to expenses resulting from hospitalizations due to complications of the disease *(69)*.

Feasibility: The GDG considered the intervention feasible and concluded that monthly injections may aid compliance compared to oral medications, provided that individuals attend clinics regularly. The practicalities of successfully implementing such a programme in very rural and remote or under-resourced areas have been shown in the trials *(66, 70)*.

Implementation considerations

- Children in different settings are exposed to various different environmental factors including viral and bacterial risks and access to other medicines, which must be taken into consideration for implementation.
- For those on oral penicillin, adherence can be improved by providing a supply for 3 months rather than a monthly prescription to reduce frequent trips to refill medication, as well as by direct observed therapy by other family members.

Research gaps

Further research is needed to clarify the role and optimize the use of prophylactic penicillin in children aged less than 5 years with SCD, particularly in the context of widespread pneumococcal vaccination and evolving antimicrobial resistance. The following were identified as priority research areas.

- Studies are needed to assess the added benefit of penicillin prophylaxis in children who have received PCV, especially as newer vaccines with broader serotype coverage (e.g. PCV20, PCV24) become available.
- Research to evaluate the effectiveness of penicillin prophylaxis in children with SCD genotypes other than HbSS, including those with more severe clinical manifestations (e.g. Hb-S/β^0-thalassaemia) and those who have undergone surgical splenectomy.
- Studies should explore how improved adherence to prophylaxis affects the incidence of invasive pneumococcal disease, mortality and health service utilization to inform policy and programmatic decisions.
- Research is needed to compare the effectiveness, acceptability and adherence of oral versus IM penicillin, including the evaluation of different oral dosing strategies (e.g. daily vs weekly).
- Further studies should assess the effectiveness and safety of alternative prophylactic agents, such as erythromycin, in children with documented penicillin allergy.
- Additional high-quality research is needed to generate evidence on contextual factors such as acceptability, feasibility, cost-effectiveness, equity and values to support implementation in diverse settings, particularly in LMICs.

3.2.3 Antibiotic prophylaxis in children aged >5 years with SCD

Recommendation 3a:

In children aged older than 5 years with SCD who have completed pneumococcal vaccination series and do not have additional risk factors, such as prior invasive pneumococcal infection or history of surgical splenectomy, prophylactic penicillin is not recommended.

Conditional recommendation, low certainty of evidence.

Recommendation 3b:

In children aged older than 5 years with SCD who have not completed pneumococcal vaccination series, or who have a history of splenectomy or prior invasive pneumococcal infection, prophylactic penicillin is suggested, regardless of vaccination status.

Conditional recommendation, low certainty of evidence.

Remarks

- Children aged older than 5 years with SCD who are unvaccinated, who have undergone surgical splenectomy or who have a history of invasive pneumococcal infection are considered at high risk of serious infections and may benefit from continued penicillin prophylaxis.
- In contrast, children aged older than 5 years with fully developed immune systems and no additional risk factors are at lower risk of pneumococcal disease, and the benefit of continued prophylaxis is likely to be minimal.
- The potential benefit of extended penicillin use in older children should be carefully weighed up against the risk of promoting antimicrobial resistance, particularly in the context of global antimicrobial stewardship efforts.
- Where vaccination records are unavailable or uncertain, health care providers should use clinical judgement based on caregiver reports and local immunization practices to determine the child's likely vaccination status.
- Children with SCD should receive and remain up to date with recommended vaccinations, including pneumococcal, Hib and meningococcal vaccines along with booster or catch-up doses as appropriate.

Justification

The GDG determined that children aged older than 5 years with SCD generally have a more mature immune system and a substantially lower risk of invasive pneumococcal disease compared to younger children. Among those who have completed the age-appropriate pneumococcal vaccination series and have no history of splenectomy or prior invasive pneumococcal infections, the continued use of penicillin prophylaxis is unlikely to provide additional benefit.

The GDG also considered the broader implications of prolonged antibiotic use, particularly in the context of antibiotic stewardship. Long-term prophylaxis may contribute to the development of antibiotic resistance, which is a growing public health concern. In the PROPS II trial, resistant organisms were isolated in a subgroup of children receiving extended penicillin prophylaxis, and observational studies have reported high rates of colonization with resistant bacteria in this population *(60, 71, 72)*.

Therefore, the decision to continue or discontinue penicillin prophylaxis in children aged older than 5 years should be individualized. For most children, the low risk of pneumococcal infection may not justify ongoing antibiotic exposure. However, continued prophylaxis may be appropriate for children at higher risk, such as those with a history of splenectomy, incomplete vaccination or previous invasive pneumococcal disease.

Summary of evidence

A systematic review conducted to inform this recommendation did not identify any new studies beyond those included in a recent high-quality Cochrane review. The Cochrane review included one RCT involving 400 children with SCD, assessing the impact of penicillin prophylaxis on invasive pneumococcal disease (IPD), mortality and adverse events *(46)*. The RCT, known as PROPS II, was conducted in the USA and enrolled children aged 5 years who had been receiving penicillin prophylaxis. Participants were randomized to either continue or discontinue penicillin prophylaxis. Children with a history of pneumococcal infection or splenectomy were excluded.

Key findings from the PROPS II trial include: invasive pneumococcal infection occurred in two of 201 participants in the continuation group and in four of 199 participants in the discontinuation group (RR: 0.50; 95% CI: 0.09–2.67), corresponding to an absolute difference of approximately 10 fewer cases per 1000 children. However, the wide confidence interval indicates high uncertainty in the effect estimate. Mortality was reported in two children in each group (RR: 0.99; 95% CI: 0.18–21.66), suggesting no meaningful difference in death rates between the groups. Adverse events were similar across both arms, with no significant differences reported.

Overall, the PROPS II trial did not demonstrate a statistically significant increase in the risk of IPD following the withdrawal of prophylactic penicillin at the age of 5 years. The absolute risk of infection in children older than 5 years was low. These findings are supported by a retrospective cohort study of children and adolescents aged 5–18 years with SCD, which found no cases of IPD among those who discontinued antimicrobial prophylaxis compared with those who continued prophylaxis *(56)*. The certainty of evidence for all critical outcomes was assessed as very low, due to imprecision and indirectness.

Benefits and desirable effects

The available evidence suggests that the risk of IPD in children with SCD older than 5 years is generally low, particularly among those who have received comprehensive care and appropriate pneumococcal vaccination. In the PROPS II trial, the absolute difference in IPD incidence between children who continued versus discontinued penicillin prophylaxis was approximately 10 fewer cases per 1000 children, a finding judged by the GDG to be clinically trivial for children without additional risk factors.

However, the GDG observed that certain subgroups of children with SCD may still benefit from continued prophylaxis beyond the age of 5 years, including those who have not received full pneumococcal vaccination, those who have undergone splenectomy or those who have a history of prior invasive pneumococcal infection. These children are at a higher risk of infection, and the GDG considered the potential benefit of continued penicillin prophylaxis in these cases to be moderate, based on clinical experience and findings from a small RCT. That trial concluded that children with SCD who had no history of severe pneumococcal infection or splenectomy, and who were receiving comprehensive care, could safely discontinue prophylactic penicillin at the age of 5 years *(54)*.

In summary, while the overall benefit of continued prophylaxis is limited in low-risk, vaccinated children, it may be more meaningful for high-risk subgroups, and clinical decisions should be tailored accordingly.

Harms and undesirable effects

The evidence from clinical trials suggests that adverse events related to penicillin prophylaxis are limited and did not differ between intervention and control arms. However, oral penicillin V and IM penicillin have known adverse effects *(61)*. In addition, in the PROPS II trial, 9% of participants with continued use of penicillin prophylaxis over the age of 5 years, in whom *S. pneumoniae* was isolated, showed intermediate or resistant pneumococci *(60)*. Based on this, the GDG judged the undesirable anticipated effects of penicillin prophylaxis among children aged older than 5 years with SCD who are vaccinated as moderate, driven by the adverse effects and the potential for antimicrobial resistance in the face of the low certainty of the impact of the intervention.

Other considerations

Preferences, values and acceptability: Due to insignificant risk of infection in children aged older than 5 years, the poor taste of oral penicillin, the possible side-effects and the cost of regular medications, the children, their caregivers and providers are less likely to value prophylaxis. However, in the high-risk group, they are more likely to value prophylaxis. The GDG judged that there was possibly important uncertainty or variability for vaccinated children aged over 5 years old, but probably no important uncertainty or variability for unvaccinated children, or those who had undergone splenectomy or who had had a prior pneumococcal infection. In terms of acceptability, patients might be less keen and, therefore, less adherent due to the poor taste of the medication or monthly painful injections. Children with SCD, parents and clinical care providers will probably not accept penicillin prophylaxis for vaccinated children aged older than 5 years without risk factors. However, since splenic function is still absent in patients with SCD aged older than 5 years, parents should be well informed and given the option to continue penicillin if desired.

Equity: Given that penicillin is widely available and relatively inexpensive, the panel judged that there would be no impact on equity. However, from the health system perspective, there will be opportunity costs due to the competing need for penicillin for other indications; for example, rheumatic fever, heart disease or syphilis.

Resources required: Penicillin is a relatively inexpensive antibiotic to implement and is mostly available in LMICs. The recommendation targets penicillin only to the high-risk group, which will be cost saving for the health system. The GDG recognized that in this at-risk population, penicillin prophylaxis would be cost-effective, due to the costs incurred by the treatment of IPD and hospital admissions.

Feasibility: Given that penicillin is widely available and relatively cheap, the panel judged that the implementation of the intervention is feasible. In addition, extensive experience with penicillin prophylaxis for rheumatic heart disease and studies involving children with SCD as part of national disease management programmes suggest that this intervention is feasible *(66, 70)*. However, considerations such as adherence to and compliance with prescribed treatment in these populations need to be taken into account.

Implementation considerations

- If the vaccination status of children is unclear, they must be fully vaccinated.
- For children living in areas with a high prevalence of meningococcal infection, this vaccine should also be given.

Research gaps

The evidence base for the continuation or discontinuation of penicillin prophylaxis in children aged older than 5 years SCD remains limited, particularly in the context of widespread pneumococcal vaccination and evolving antimicrobial resistance. The following research priorities have been identified.

- RCTs are needed to assess the effectiveness of continued penicillin prophylaxis in fully vaccinated children aged older than 5 years without additional risk factors. These studies should evaluate clinical outcomes such as the incidence of IPD, mortality and health service utilization.
- Comparative effectiveness studies should explore the benefits and risks of extended prophylaxis in high-risk subgroups, including children with a history of splenectomy or prior invasive pneumococcal infection, and those with incomplete or uncertain vaccination status.
- Research on antimicrobial resistance patterns associated with prolonged penicillin use in older children is needed to inform antimicrobial stewardship strategies.
- Implementation research should assess the feasibility, acceptability and cost-effectiveness of different prophylaxis strategies (e.g. oral vs IM administration) in various health system contexts, particularly in LMICs.

3.2.4 Alternative antibiotics for prophylaxis to prevent pneumococcal infection

No recommendation:

WHO makes no recommendation on the use of antibiotics other than penicillin for pneumococcal prophylaxis in children and adolescents (aged 0–19 years) with SCD, due to insufficient evidence.

No recommendation due to insufficient evidence.

Remarks

- There is currently insufficient evidence to support an evidence-based recommendation regarding the use of alternative antibiotics to penicillin for pneumococcal prophylaxis in children and adolescents with SCD.
- Further research is needed to evaluate the efficacy and safety of non-penicillin antibiotic options in this population.

Justification

The GDG reviewed the available evidence on the use of antibiotics other than penicillin for pneumococcal prophylaxis in children and adolescents with SCD. The systematic review identified only one small nonrandomized cohort study involving 94 children aged less than 3 years, which compared penicillin to spiramycin *(73)*. In this study, children in the spiramycin group had previously received penicillin before switching. The results showed no cases of pneumococcal infection in the penicillin group and one case of septicaemia in the spiramycin group; no deaths were reported. Due to the study's small sample size, nonrandomized design and limited outcome data, the evidence was considered inconclusive.

Beyond this single study, no additional relevant or high-quality evidence was identified. The GDG concluded that the available data were insufficient to determine the efficacy or safety of alternative antibiotics for pneumococcal prophylaxis in this population. Concerns about antimicrobial resistance, as well as the cost and feasibility of long-term use of non-penicillin agents further contributed to the uncertainty. As a result, the GDG decided not to issue a recommendation at this time and placed this PICO question on hold until more robust evidence becomes available, including indirect evidence from other relevant populations and settings.

Research gaps

There is currently insufficient evidence to support the use of antibiotics other than penicillin for pneumococcal prophylaxis in children and adolescents with SCD. The available data are limited to a single small nonrandomized study (NRS), and no high-quality comparative evidence exists. To inform future recommendations, the following research priorities were identified.

- RCTs comparing the efficacy and safety of alternative antibiotics to penicillin for pneumococcal prophylaxis in children with SCD, including those with penicillin allergy.
- Pharmacovigilance and antimicrobial resistance studies to assess the long-term safety, resistance patterns and public health implications of using non-penicillin antibiotics in this population.
- Cost-effectiveness analyses of alternative prophylactic regimens, particularly in LMICs, where access to some of these antibiotics may be limited.
- Implementation research to evaluate the feasibility, acceptability and adherence to alternative antibiotic regimens in diverse health system contexts.
- Indirect evidence synthesis from other high-risk paediatric populations (e.g. rheumatic fever or heart disease, asplenic children, immunocompromised patients) to inform interim guidance while awaiting direct evidence in children with SCD.

These research efforts are essential to guide future updates to this recommendation and ensure safe, effective and context-appropriate prophylactic strategies for children and adolescents with SCD.

3.3 Hydroxyurea therapy for the management of SCD

3.3.1 Background

Comprehensive care has significantly decreased mortality in children with SCD, although complications continue to cause significant morbidity and mortality *(42, 74)*. Hydroxyurea, also known as hydroxycarbamide, is an oral antineoplastic drug and an inhibitor of ribonucleotide reductase that has been shown to have many beneficial effects for treating SCD *(75)*. These effects include increasing HbF concentration in RBCs, improving metabolism of nitric oxide and reducing red cell–endothelial interaction and erythrocyte density *(75-79)*. These disease-modifying effects have been shown to decrease episodes of pain, ACS, hospital admissions and the need for transfusions *(80-84)*. In high-income countries, hydroxyurea is the first-line primary disease-modifying therapy for patients with SCD regardless of clinical severity. Its efficacy and effectiveness in children and adults with SCD have also been shown even in low-resource settings *(85-87)*.

Although the evidence of efficacy is clear, in addition to resource constraints in LMICs, there remain concerns about side-effects that have been a barrier to its widespread use and adherence, *(88-90)*. These side-effects include dose-related haemopoietic suppression leading to neutropenia, thrombocytopenia and reticulocytopenia *(77)*. Furthermore, there are concerns regarding the potential for increased risk of cancer or teratogenic effects due to the origins of hydroxyurea as a chemotherapeutic medication *(91)*. However, long-term studies on patients taking hydroxyurea have demonstrated a good safety profile for low-dose hydroxyurea and there is no evidence for the theoretical concerns of infertility, teratogenicity, mutagenicity or carcinogenicity *(76, 84)*. The majority of patients in LMICs with SCD still do not have access to hydroxyurea therapy due to some of these concerns *(92, 93)*.

Despite the current evidence to support the use of hydroxyurea, it is important to examine and evaluate its clinical use, and its effectiveness and safety in children and adolescents with SCD, particularly in low-resource settings.

Recommendation 4:

In children and adolescents (aged 9 months to 19 years) with SCA, hydroxyurea therapy is recommended regardless of clinical severity.

Strong recommendation, low certainty of evidence.

Remarks

- Appropriate dosing and regular monitoring are essential to optimize the therapeutic benefits of hydroxyurea and minimize the risk of adverse events.
- Health care providers should offer clear, age-appropriate information to caregivers, children and adolescents to support informed decision-making and adherence.
- Acceptability and uptake of hydroxyurea can be enhanced through effective communication, counselling and advocacy by health care providers.
- Adolescents receiving hydroxyurea should be counselled on the need for contraception, as hydroxyurea is contraindicated during the first trimester of pregnancy due to potential embryo-fetal toxicity.

3.3.2 Justification

The GDG considered the substantial burden of disease in children and adolescents with SCA, including recurrent VOCs, ACS stroke and other severe complications. Evidence shows that hydroxyurea significantly reduces the frequency of ACS, dactylitis, painful crises and hospitalizations, with moderate certainty of evidence. For other outcomes, such as sepsis or bacteraemia, stroke, anaemia and transfusion need, the certainty of evidence was low. Despite this, the GDG made a strong recommendation based on the overall balance of benefits and risks. Hydroxyurea provides clinically meaningful reductions in acute complications and improves quality of life. The harms of not treating were judged to be substantial, given the high disease burden. Hydroxyurea also has a well-established safety profile, with serious adverse events occurring rarely when appropriately monitored. The GDG judged that most caregivers and patients would place a high value on reducing acute complications, ACS, painful episodes and hospitalizations. Furthermore, hydroxyurea is an oral, once-daily medication that is feasible to administer and monitor in most settings, and its use may help reduce health inequities by improving access to effective care.

Despite uncertainties around mortality benefits, long-term safety and optimal dosing, the GDG determined that hydroxyurea therapy delivers moderate yet meaningful clinical gains, most notably reducing acute sickle-cell related complications, hospitalizations and health care utilization, while improving haemoglobin levels and overall quality of life. Balancing these advantages against the low to moderate certainty of current evidence, the GDG issued a strong recommendation to offer hydroxyurea to every child and adolescent aged 9 months to 19 years with SCA, regardless of baseline clinical severity, to lessen disease burden and enhance long-term outcomes.

3.3.3 Summary of evidence

The systematic review identified a recent Cochrane review that included a total of eight RCTs and 12 NRSs involving children and adolescents with SCA *(94)*. The eight RCTs were conducted primarily in high-income countries, enrolling a total of 890 participants aged 9 months to 18 years. Hydroxyurea dosages ranged from 10 mg/kg to 22.5 mg/kg per day, with one trial escalating to a maximum of 35 mg/kg per day. The 12 NRSs included 3729 participants from both high-income countries and LMICs, with hydroxyurea dosages ranging from 9.23 mg/kg per day to 27.2 mg/kg per day. Comparisons in the RCT studies included: hydroxyurea versus placebo; hydroxyurea versus no hydroxyurea; hydroxyurea and phlebotomy versus transfusion and chelation therapy (for stroke prevention); and hydroxyurea versus observation (in children at an increased risk of stroke) *(94)*. In the NRS, five studies compared groups of hydroxyurea therapy versus no hydroxyurea therapy, and seven studies used before and after designs assessing hydroxyurea therapy in the same population *(94)*.

Pooled analysis of the RCTs showed moderate certainty of evidence for a reduction in several clinically important outcomes among children receiving hydroxyurea therapy compared with placebo or no hydroxyurea, such as ACS (RR: 0.40; 95% CI: 0.18–0.88), dactylitis (RR: 0.51; 95% CI: 0.39–0.67), painful crises (RR: 3.37; 95% CI: 1.59–7.11) and hospitalization (RR: 0.64; 95% CI: 0.43–0.95), but low certainty of evidence for sepsis or bacteraemia (RR: 0.44; 95% CI: 0.20–0.99), blood transfusion (RR: 0.64; 95% CI: 0.43–0.95) and stroke *(81, 95-98)*. In addition, both the RCTs and NRSs consistently showed a significant increase in HbF levels in the hydroxyurea group, with the NRS reporting increases of over 15%. No statistically significant difference in mortality was observed in the RCTs. However, the REACH trial, a large NRS, reported a reduction in mortality rates after 31–36 months of hydroxyurea therapy (from 3.6 to 1.1 deaths per 100 patient-years) *(86)*. There was insufficient evidence to determine whether a standard dose or dose escalation to the maximum-tolerated dose is preferable.

Adverse events associated with hydroxyurea therapy included increased rates of reticulocytopenia, neutropenia and anaemia, particularly in studies using dose escalation, but no increase in rates of thrombocytopenia and infection *(81, 86, 97, 98)*. The BABY HUG study, which used a standard dose of 20 mg/kg, reported increased neutropenia but no increase in thrombocytopenia or infections *(94)*. Long-term observational data over 15 years of hydroxyurea use did not raise any safety concerns *(84)*.

Overall, the evidence supports the clinical effectiveness of hydroxyurea therapy in reducing acute complications of SCA, with moderate certainty for key outcomes. Although the mortality benefits are less certain, observational data suggest potential long-term survival advantages. Safety concerns appear manageable, particularly with standard dosing, although further research is needed to clarify optimal dosing strategies.

Benefits and desirable effects

Hydroxyurea therapy offers moderate potential benefits for children and adolescents aged 9 months to 18 years with SCA. Evidence from RCTs and NRSs indicates that hydroxyurea therapy is associated with: significant reductions in the frequency of ACS, dactylitis, painful crises and hospitalization; possible reductions in other acute complications including sepsis or bacteraemia, stroke, anaemia, and the need for blood transfusion; increased levels of HbF, which may contribute to improved clinical outcomes; and a potential survival benefit, as suggested by observational data, although mortality effects remain uncertain.

The GDG judged the certainty of the evidence as moderate for primary outcomes of ACS, dactylitis painful crises and hospitalization, as low for sepsis or bacteraemia, stroke, anaemia and blood transfusion, and as very low for increase in HbF, mortality reduction and adverse events, where data were limited and imprecise.

The GDG agreed that the overall clinical benefits of hydroxyurea therapy in children and adolescents aged 9 months to 19 years with SCA were moderate even though the magnitude of its effect on mortality was low. The GDG determined that hydroxyurea reduces the frequency of SCD-related complications (e.g. pain, dactylitis, ACS, anaemia) and the need for blood transfusions and hospitalization.

Harms and undesirable effects

Harms were identified as trivial. There were no severe adverse events reported in the included studies. The GDG noted increased rates of gastroenteritis, reticulocytopenia, neutropenia and anaemia. However, these incidents mainly occurred in studies with dose escalation, and there was no increase in thrombocytopenia events or in the number of infections in the hydroxyurea group compared to the placebo group. There was no reported increase in other known adverse events related to hydroxyurea such as hair loss, skin rash, fever and gastrointestinal disturbance.

The GDG also recognized the theoretical concerns of infertility, teratogenicity or mutagenicity potentially associated with hydroxyurea and noted that these have not been documented in humans. The GDG determined that these theoretical concerns had no supporting evidence and should not affect the decision to use hydroxyurea therapy in children with SCA. However, patients and caregivers should be provided with appropriate information for decision-making, and there is a need for appropriate dosing and monitoring strategies to optimize benefits while avoiding the toxicity of hydroxyurea.

Other considerations

Preferences, values and acceptability: Patients and caregivers may value the reduction in pain and life-threatening acute complications. However, they may be fearful of the potential risks and long-term effects of hydroxyurea, including its effects on fertility and reproduction *(99)*. In addition, patients on complex medication regimens might not value the addition of more medication to their regimen *(100, 101)*. Although most clinicians and physicians might value the clinical efficacy of hydroxyurea, some might have concerns about its long-term safety and toxicity that could limit its prescription *(102)*. On acceptability, the GDG determined that treatment with hydroxyurea is probably acceptable to key stakeholders (e.g. patients, caregivers, clinicians, pharmacists, governments) because of the expected clinical improvements; however, it recognizes the variability introduced by the uncertain side-effects, especially for persons of reproductive age *(89, 100)*. However, inadequate knowledge of the clinical benefits and safety, the non-availability and cost-effectiveness of hydroxyurea as well as the lack of evidence-based treatment guidelines may play a major role in acceptability.

Resources required: Studies reported significantly fewer transfusions, hospitalizations and emergency room visits, and shorter admissions. Aside from the cost of drug therapy, hydroxyurea use can reduce health care resource utilization. Compared with no use of the drug, hydroxyurea use could lead to substantial net savings per patient, while reducing disease morbidity and mortality and increasing quality of life *(103)*. The added cost of hydroxyurea medication and outpatient care for safety monitoring is relatively low compared with the reduction in hospital costs *(76, 103, 104)*.

Equity: The GDG determined that treatment with hydroxyurea has the potential to increase equity. It observed that hydroxyurea is an oral medication that is relatively low in price and easily administered, and that can be provided at all levels of the health system which will increase access. In addition, its use will significantly reduce the incidence of acute and chronic complications leading to better quality of life for all SCA patients.

Feasibility: The GDG determined that it is feasible to implement hydroxyurea therapy for all children aged 9 months to 18 years at all levels of the health system. However, feasibility may vary depending on health system capacity, regulatory frameworks and resource availability.

3.3.4 Implementation considerations

Effective implementation of hydroxyurea therapy requires not only policy and regulatory alignment but also practical measures to ensure safety, accessibility and acceptability. These include strengthening health system capacity, integrating infection prevention strategies, establishing monitoring protocols and creating mechanisms such as safety registries to track outcomes. The considerations outlined below provide a comprehensive framework for countries to adapt and operationalize hydroxyurea use in a way that is equitable, feasible and responsive to local needs. The following factors should be addressed.

- Hydroxyurea should be included on the national paediatric essential medicine list for SCA treatment to ensure that national health policies and regulations allow all qualified clinicians to prescribe hydroxyurea for SCA patients.
- Ensure availability of paediatric dosage formulations and improve affordability and access, particularly in rural areas and for lower income or vulnerable populations.
- Educate health care workers, including specialists, on the safety, benefits and appropriate use of hydroxyurea therapy in children with SCA.
- Establish protocols for regular blood counts and infection surveillance to detect neutropenia and early signs of sepsis or bacteraemia.
- Provide guidance on low-dose initiation at primary care facilities with referral linkages for dose adjustment and laboratory monitoring.
- Increase acceptability through advocacy and provision of clear, culturally appropriate information to caregivers for informed decision-making.
- Maintain full vaccination schedules and prophylactic antibiotics where indicated, and educate caregivers on the prompt recognition of infection symptoms and timely care-seeking.
- Establish national or regional registries to monitor adverse events, infection rates, stroke incidence, anaemia trends and transfusion needs during hydroxyurea therapy.

Furthermore, the GDG noted that, at a policy level, hydroxyurea therapy may not be considered acceptable in some countries because of opportunity costs, particularly where the prevalence of SCA is low. In such settings, governments must weigh the costs of establishing and sustaining national systems for hydroxyurea therapy against competing priorities within constrained health budgets.

3.3.5 Research gaps

Although hydroxyurea is strongly recommended for children and adolescents with SCA, several important questions remain unanswered regarding its long-term use, optimal implementation and applicability across diverse populations and settings. The following areas were identified as priorities for future research.

- High-quality longitudinal studies are needed to assess the long-term effects of hydroxyurea, particularly its impact on growth, fertility and reproductive health in adolescents of childbearing age. Research should also explore the relationships between cumulative dose, duration of therapy and potential toxicities.
- Additional studies should evaluate hydroxyurea's effect on sepsis or bacteraemia, stroke incidence, anaemia severity and transfusion requirements. Comparative effectiveness research is needed to determine whether hydroxyurea reduces transfusion burden and stroke risk compared to chronic transfusion strategies, and whether it influences infection susceptibility.

- Additional high-quality research is needed to generate evidence on contextual factors that influence the successful use of hydroxyurea, including acceptability, feasibility, adherence, cost-effectiveness, health system capacity and equity. This is particularly important in LMICs, where access to regular monitoring and laboratory services may be limited.
- Most RCTs to date have focused on individuals with the HbSS or HbS/β^0-thalassemia genotypes. Further studies are needed to evaluate the safety and efficacy of hydroxyurea in individuals with other genotypes such as HbSC or HbSβ^0 thalassaemia, who may have different clinical trajectories and treatment needs.
- Research should explore optimal dosing regimens, including fixed-dose versus dose-escalation strategies, and simplified monitoring protocols that could improve feasibility and uptake in resource-limited settings.
- Qualitative and mixed-methods studies are needed to better understand the values, preferences, and experiences of patients and caregivers regarding hydroxyurea use, including barriers to adherence and strategies to support informed decision-making.

These research efforts are essential to refine clinical guidance, support equitable access and ensure that hydroxyurea therapy is used safely and effectively across all settings.

3.4 NSAIDs, paracetamol, opioids and blood transfusion in the management of pain

3.4.1 Background

Pain is a major cause of morbidity for individuals living with SCD from infancy through to adulthood. It manifests as recurrent acute and/chronic pain, or as acute-on-chronic pain episodes. Pain causes significant physical and psychological morbidity, and frequent health care utilization *(105-107)*. VOC pain is most common in children and adolescents, and is a multifactorial process *(105)*. It involves not only occlusion of small blood vessels by sickled RBCs and adherent blood cells, but also large-vessel intimal hyperplasia, thrombosis and bone marrow fat embolization, leading to hypoxia, ischaemia, and tissue damage, inflammation and nervous system sensitization *(108-110)*. It is this combination of hypoxic reperfusion injury, ischaemic tissue damage and inflammation that makes SCD pain unique and a clinical challenge *(111, 112)*. Recurrent episodes of hypoxic–ischaemic reperfusion injury to bones and tissues due to VOCs result in inflammation and tissue damage leading to recurrent chronic pain. The optimal management of pain requires multiple interventions such as pharmacological, nonpharmacological and preventive therapeutic interventions *(113-115)*.

NSAIDs, opioids and their combinations are the mainstay of pain treatment, but additional supportive therapies include hydration, local pain control, muscle relaxants and nonpharmacological approaches *(114)*. In a majority of children and adolescents with acute VOCs, their pain is managed at home before presenting for medical attention *(105, 106, 116)*. Acute painful episodes require a balance between achieving efficacy and preventing adverse events *(117)*. Adverse events for opioids include respiratory depression, constipation, vomiting, nausea, pruritus and hives, and addiction and withdrawals. Although the NSAIDs commonly used can produce a ceiling effect and systemic side-effects *(118)*, the risk of adverse effects can be minimized by prescribing the lowest dose for the shortest duration possible to control the symptoms. Considering the detrimental effects pain episodes have on patients with SCD, and the advantages and pitfalls of both NSAIDs and opioids, it is important to address the optimal management of acute pain and chronic pain.

Regular RBC transfusion therapy has also been used for the prevention and treatment of recurrent acute and chronic pain *(98, 119-121)*. Blood transfusions improve blood oxygen content, decrease HbS-containing RBCs and increase HbA RBCs with normal oxygen affinity which may reduce VOC episodes *(122-124)*. However, despite the widespread practice of regular blood transfusions, there is still variability in clinical practice *(119, 121)*. This is driven by a paucity of data on the indications, adverse events of chronic transfusion and the availability of resources to ensure safe chronic RBC transfusion *(125, 126)*. In addition, there is need for regular iron overload monitoring, and treatment with, and patient adherence to, iron chelation therapy *(127-129)*. Hence the need to evaluate the evidence for the efficacy and/or effectiveness, and safety of regular/chronic transfusion therapy as a treatment for recurrent acute and chronic pain especially in LMICs.

3.4.2 NSAIDs for the management of acute pain

Recommendation 5:

In children and adolescents (aged 0–19 years) with SCD experiencing acute painful crises, the use of NSAIDs is suggested for initial pain management.

Conditional recommendation, very low certainty of evidence.

Remarks

- The GDG noted uncertainty regarding the generalizability of evidence from intravenous (IV) ketorolac to oral NSAIDs. However, oral NSAIDs were considered a more feasible and accessible option, particularly in primary care settings where IV formulations may not be available.
- When NSAIDs alone are insufficient for managing moderate to severe acute pain, a stepwise approach may be used: starting with paracetamol plus NSAIDs, followed by escalation to opioids if pain remains uncontrolled.
- Health care providers should conduct individualized risk assessments and clearly explain the potential benefits and harms of NSAIDs versus opioids to the children, adolescents and their caregivers to support informed decision-making.
- IV opioids may be a reasonable option when IV NSAIDs are unavailable or when rapid pain relief is prioritized. Patients who prioritize immediate pain relief over concerns about opioid-related side-effects may reasonably choose opioid analgesics for acute pain management.

Justification

Recurrent episodes of acute severe pain are a hallmark of SCD, and a leading cause of health care utilization in affected children and adolescents. The GDG recognized that all stakeholders – patients, caregivers and health care providers – place high value on rapid and effective pain relief.

The evidence from RCTs suggests that NSAIDs, particularly IV ketorolac, may reduce pain intensity and opioid requirements. However, the certainty of evidence was judged to be very low due to indirectness (limited data on oral NSAIDs), imprecision and risk of bias. Despite the very low certainty of evidence, the GDG made a conditional recommendation based on several key considerations. NSAIDs may offer meaningful pain relief and reduce the need for opioids – benefits that are highly valued by both patients and providers. Although NSAIDs carry a small risk of renal toxicity, particularly in dehydrated or high-risk individuals, this risk can be managed with appropriate caution. Oral NSAIDs are also widely available, affordable and easy to administer, making them a feasible option in various settings, including at home. Furthermore, the GDG judged that most patients and caregivers would prioritize the potential for effective pain relief and reduced opioid exposure, even in the face of uncertainty in the evidence.

Given the balance of potential benefits and harms, and the very low certainty of evidence, the GDG issued a conditional recommendation in favour of NSAID use for initial pain management in acute SCD crises. However, NSAIDs should be used cautiously in this population given the risk of kidney injury and the very low certainty of evidence.

Summary of evidence

The systematic review identified two RCTs with a total of 70 children and adolescents aged 3–19 years with SCD. One study was a randomized, single-blinded study conducted in the USA comparing the safety and efficacy of ketorolac tromethamine with meperidine in 20 children aged 10 years or older with VOC *(130)*. The other study, a randomized, open-label single-centre trial carried out in India, assessed the efficacy and safety of IV ketorolac compared with IV morphine in 50 children aged 3–15 years with severe VOC pain *(131)*. The primary outcomes of both studies were change in pain scores and adverse events; however, a meta-analysis was not possible.

The study from the USA reported statistically significantly larger decreases in the pain scores over the 150 min observation period in the group receiving ketorolac tromethamine compared with those receiving meperidine ($P < 0.01$) but the pain scores were comparable after crossover *(130)*. In this study, there were significantly more discharges in the NSAID group compared to the opioid group ($P < 0.01$). However, the study in India, which compared ketorolac with morphine, did not find statistically significant differences between the two treatment groups *(131)*. There was low certainty evidence from these RCTs which suggests that NSAIDs were more likely to result in patients being pain free after treatment, although a limited number of events were observed. Both studies reported minor but lower incidences of adverse events in the NSAID groups compared to the opioids groups, with low certainty of evidence that NSAIDs may result in fewer adverse events compared to opioids.

Benefits and desirable effects

The potential benefits of the use of NSAIDs to treat acute pain in children and adolescents with SCD are moderate. The desirable effects include improved pain control, reduced opioid utilization and decreased length of stay. The GDG judged that the 2-point reduction of pain score and the 142 per 1000 more pain-free patients at 2.5 hours was in favour of NSAIDs, although with a low level of certainty of evidence *(130)*. In addition, NSAIDs may offer a more favourable safety and efficacy profile when managing pain in patients with SCD despite the very low certainty of evidence. The GDG noted that NSAIDs provided more pain relief or equal relief compared to opioids in two studies, resulted in fewer unwanted effects when compared to opioids, including sedation and dizziness, and resulted in more discharges.

The GDG determined that NSAIDs may be an effective method of managing acute pain in patients with SCD when compared to opioids alone, especially when considering the efficacy of the medications, differences in unwanted effects and hospitalization rates. The GDG noted that while the evidence is from IV ketorolac, oral NSAIDs might be preferred to IV NSAIDs that are more likely to be unavailable in many settings. However, the GDG also noted that in some cases NSAIDs alone may not be sufficient to control severe acute pain and suggested a sequential escalation that starts with paracetamol and NSAIDs, then if pain is not controlled, to go for opioids.

Harms and undesirable effects

Harms were identified as small because there were only minor adverse events in both arms with 223 fewer adverse events per 1000 in favour of NSAIDs. However, the GDG noted that because of the small sample size, rare adverse events are more likely to have been missed; for example, opioids are known to cause respiratory depression, constipation, dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus and vomiting *(132)*. NSAIDs may cause gastrointestinal ulcers, serious cardiovascular events, hypertension, acute kidney injury and worsening of pre-existing heart failure *(133-135)*. Caution is needed in children with sickle-cell nephropathy, as acute kidney injury is a clinically recognized adverse event following NSAIDs, especially among patients with nephropathy due to cumulative nephrotoxicity *(136)*. The different adverse event profiles of NSAIDs and opioids should be considered when initiating treatment in children and adolescents with SCD.

Other considerations

Preferences, values and acceptability: The GDG determined that there is no significant uncertainty or variability. Patients, care givers and health care providers value reducing pain intensity and the distress associated with experiencing pain and reducing the need for the utilization of health services for patients with SCD. In addition, both patients and health care providers would value the immediate decrease in pain provided by NSAIDs, and a decrease in the consumption of opioids and the undesirable side-effects which occur because of the use of opioids. The GDG determined that this intervention is acceptable to key stakeholders, such as health educators and counsellors, patients and caregivers, and health care providers (clinicians, pharmacists, etc.), driven by the need to reduce pain and the consumption of opioids.

Resources required: There were no specific studies that looked at the resources required; however, the GDG noted that IV NSAIDs may be more expensive than IV opioids in many countries. Costs might be mitigated by the use of oral NSAIDs and health insurance coverage for NSAIDs in some countries.

Equity: The GDG noted that NSAIDs, both IV and oral, are available in LMIC settings; therefore, making use of this intervention will probably lead to increased equity.

Feasibility: The GDG determined that this intervention is probably feasible to implement.

Implementation considerations

- Patients and their caregivers should be educated to start with oral treatment using paracetamol and/or NSAIDs at home, as well as when to seek further evaluation and escalation of the treatment with opioids when oral analgesia has not been effective in controlling pain.
- Individualized patient protocols should be used to guide pain treatment. Health care providers should be aware of the adverse effects associated with both NSAIDs and opioids.
- Opioids should be used at the lowest effective dose for the shortest duration possible, although patients experiencing acute painful crises may require aggressive initial opioid doses to achieve adequate pain control.

Research gaps

The evidence supporting the use of NSAIDs for initial pain management in children and adolescents with SCD remains limited, particularly regarding oral formulations and comparative effectiveness. To strengthen the evidence base and inform future updates to this recommendation, the following research priorities were identified.

- Comparative effectiveness studies are needed to evaluate the use of oral NSAIDs versus opioids for the initial management of acute pain in children and adolescents with SCD, including assessments of pain relief, functional outcomes and patient satisfaction.
- Head-to-head trials of different NSAIDs should be conducted to compare efficacy, safety and tolerability profiles. These studies should also aim to standardize outcome measures for pain intensity, duration and functional recovery to improve comparability across trials.
- Optimal dosing strategies and treatment durations for NSAIDs in younger age groups remain unclear. Further research is needed to determine age-appropriate dosing schedules, duration of therapy and monitoring protocols to ensure both safety and effectiveness.
- Implementation research is needed to explore the feasibility, acceptability and adherence to NSAID-based pain management protocols in various health system contexts, especially in low-resource settings.

3.4.3 NSAIDs plus opioids for the management of acute pain

Recommendation 6:

In children and adolescents (aged 0–19 years) with SCD, the use of NSAIDs in combination with opioids is suggested for the management of moderate to severe acute pain, rather than opioids alone.

Conditional recommendation, low certainty of evidence.

Remarks

- The GDG acknowledged that in real-world settings, this recommendation may be implemented through a stepwise approach, initiating treatment with NSAIDs and escalating to combination therapy with opioids if pain is not adequately controlled.
- The decision to use NSAIDs in combination with opioids should be guided by the patient's baseline pain severity, individual preferences and a clear explanation of the potential benefits and harms of both NSAID and opioid therapies.
- Shared decision-making between health care providers, patients and caregivers is essential to ensure safe, effective and acceptable pain management.

Justification

The GDG made a conditional recommendation in favour of using NSAIDs and opioids for the management of moderate to severe acute pain in children and adolescents with SCD. This recommendation was primarily driven by evidence suggesting that combination therapy may reduce pain scores and frequency of hospitalizations compared to opioids alone. Although the certainty of evidence was low, the GDG judged that the desirable effects, particularly improved pain control and reduced health care utilization, outweighed the potential harms.

Additionally, the combination approach may help reduce overall opioid consumption, which is valued by patients, caregivers and health care providers due to concerns about opioid-related side-effects and dependency. These considerations, along with the feasibility of implementing a stepwise approach in clinical practice, supported the conditional recommendation.

Summary of evidence

The systematic review identified only two studies, one RCT and one NRS that compared the use of NSAIDs and opioid combinations versus opioid monotherapy *(137, 138)*. A retrospective chart review study was conducted in Canada to document pain scores, pain regimens and hospitalization rates for 41 patients with SCD-related pain who received combination (NSAID + opioid) therapy or opioids alone in the emergency department *(138)*. In this study, a higher percentage of patients who received opioids alone as initial treatment were hospitalized as compared with those who initially received combination treatment (P = 0.0085). In the USA, an RCT was conducted that compared a single dose of IV ketorolac or placebo in combination with morphine in 47 children who presented with VOC pain in the emergency department *(137)*. Both groups experienced reductions in pain scores, but the reduction was greater among patients in the ketorolac group compared to the placebo group. However, this reduction did not significantly differ between groups at any point during the duration of the study. The mean doses of morphine administered were 0.04 mg/kg lower in the NSAID arm (0.28 mg/kg; standard deviation (SD): 0.08 mg/kg) compared with the opioids-alone arm (0.28 mg/kg; SD: 0.08 mg/kg), although the differences were not significant (P = 0.118). These findings suggest that the combination of NSAIDs and opioids may offer potential advantages over opioid monotherapy in the management of pain in children with SCD. Neither study reported any significant safety concerns associated with the use of combination therapy.

Benefits and desirable effects

The GDG judged that the combination of NSAIDs and opioids likely provides moderate additional benefits compared to opioid monotherapy for the management of moderate to severe pain in children and adolescents with SCD. This decision was primarily informed by evidence indicating a reduction in hospitalizations (116 fewer per 1000 patients and a modest improvement in pain scores (mean reduction: 1.41 points)) in favour of combination therapy following emergency department visits *(137)*. Although the certainty of evidence was low, these outcomes were considered clinically meaningful. Furthermore, evidence from studies in children with other conditions supports the additive effect of NSAIDs when used alongside opioids, including reduced pain intensity and decreased opioid consumption *(139)*. These findings suggest that NSAID and opioid combination therapy may offer potential advantages over opioid monotherapy, despite some variability in study results.

Harms and undesirable effects

Harms were identified as small. This was prompted by the absence of reported adverse events in both studies, while taking into consideration the known potential adverse events of NSAIDs and opioids. The GDG noted that, because of the small sample size, rare adverse events are likely to be missed. NSAIDs and opioids have different adverse event profiles which should be considered when initiating these treatments in patients. Opioids may cause respiratory depression, constipation, dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus and vomiting. In addition, acute kidney injury is a potentially serious adverse event following NSAID use, especially among patients with prior history of nephropathy. It is a clinically recognized adverse event, and caution is needed in children with sickle-cell nephropathy due to cumulative nephrotoxicity.

Other considerations

Preferences, values and acceptability: No studies were evaluated as part of this review. The GDG decided there was likely to be no significant uncertainty or variability in how much people value the main outcome. Pain treatment and health care utilization are likely to be important to patients and caregivers. The GDG recognized that families would greatly value this recommendation due to their concern about the pain that their children with SCD have. Patients, families and health care providers will also value a decrease in the consumption of opioids and the undesirable side-effects associated with the use of opioid analgesics, such as respiratory depression, constipation, opioid dependence and stigma from opioid use. The GDG decided this intervention would be acceptable to key stakeholders including patients and caregivers, health care providers and pharmacists. However, it will require advocacy to convince some health care workers to use combination therapy as a first-line therapy due to their reluctance to use opioids.

Resources required: The resource requirements were considered as moderate, although no studies on cost or cost-effectiveness were evaluated. This judgement was prompted by the requirement for the use of the IV route which requires skilled health care personnel to both administer and monitor vital signs and adverse events. Although there were no differences found in the rates of hospital admission and emergency department revisits in the included RCTs, the addition of NSAIDs to opioids has been shown to reduce inpatient hospital costs by over 40% in paediatric patients *(137, 139)*. The GDG also recognized that IV NSAIDs may be more expensive than IV opioids in many LMICs, and, when combined with opioids, the cost will be higher.

Equity: The intervention would probably increase health equity as SCD primarily affects individuals in LMICs and racial and ethnic minorities in high-income countries *(4)*. Implementing effective pain management strategies may reduce unnecessary health care resource utilization and its associated disparities. The GDG judged that NSAID and opioid IV formulations are more difficult to obtain in LMIC settings and having such global recommendations may promote policies in LMICs to increase access to these drugs. Adding NSAIDs to opioids will increase equity by allowing patients to have a better quality of life as a benefit of having the treatment to reduce pain.

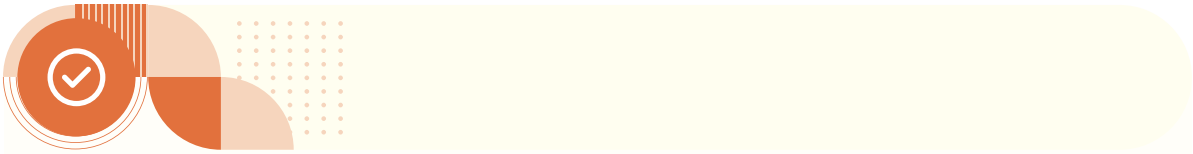
Feasibility: The GDG determined that this intervention is probably feasible to implement. However, health care providers should be aware of the adverse effects of both NSAIDs and opioids, which are often necessary for the treatment of acute painful crises in patients with SCD. In addition, opioids should be used at the lowest effective dose for the shortest duration possible, although patients with acute painful crises may require aggressive initial opioid doses to achieve adequate pain control.

Research gaps

The evidence supporting the combined use of NSAIDs and opioids for the management of moderate to severe acute pain in children and adolescents with SCD remains limited. To strengthen the evidence base and inform future updates to this recommendation, the following research priorities were identified.

- Multicentre RCTs comparing different NSAID types, routes of administration (oral vs IV), dosing regimens and treatment durations when used in combination with opioids for acute pain management.
- Research on contextual and implementation factors, including acceptability, feasibility, adherence, resource use and equity to inform real-world applications of combination therapy in diverse health care settings.
- Cost and cost-effectiveness analyses studies of combination therapy versus opioid monotherapy, particularly in LMICs, to support health system planning and resource allocation.
- Evaluation of different NSAID dosing strategies, including daily versus intermittent dosing, to optimize pain control while minimizing adverse effects and improving adherence.
- Longitudinal studies to assess whether the addition of NSAIDs to opioid regimens reduces cumulative opioid exposure, shortens hospital stays or lowers emergency department revisit rates in children with SCD.

3.4.4 Opioids plus paracetamol for the management of acute pain



Recommendation 7:

In children and adolescents (aged 0–19 years) with SCD, the use of opioids alone is suggested for acute pain management rather than paracetamol plus opioids.

Conditional recommendation, very low certainty of evidence.

Remarks

- This recommendation is based on the evidence from studies using IV paracetamol in combination with opioids at the initiation of treatment, which did not demonstrate additional benefit compared to opioids alone.
- Health care providers should engage in shared decision-making with children, adolescents and their caregivers regarding the use of paracetamol versus opioids for managing pain at home, considering individual preferences, prior experiences and potential risks.

Justification

The GDG made a conditional recommendation against the routine addition of paracetamol to opioids for the management of acute pain in children and adolescents with SCD. This decision was based on very low-certainty evidence indicating no clear additional clinical benefit from combining paracetamol with opioids in terms of short-term pain reduction, which is typically prioritized in acute pain episodes.

Furthermore, the addition of paracetamol did not result in meaningful changes in opioid consumption, hospital admissions or adverse events. Although oral paracetamol is inexpensive and generally well accepted by families, the GDG concluded that its routine use alongside opioids does not provide added value in this context. Therefore, opioids alone are suggested for managing acute pain in this population.

Summary of evidence

The systematic review identified one RCT and one NRS conducted in the USA. The retrospective NRS was conducted in children and adolescents (aged 2–19 years) with SCD admitted to the hospital for pain management and compared 28 children who received opioids alone to 18 children who received a combination of opioids and paracetamol. The study showed that the addition of paracetamol to opioids further reduced pain scores by 0.8 out of 10, representing a 14.8% relative reduction in pain, and showed a trend for reduced overall and daily opioid exposure. Fewer adverse events were reported in the combination group compared to opioid-only patients (50% vs 61%), which is a relative reduction of 18% *(140)*. The RCT was conducted in children and adolescents (aged 4–16 years) with SCD pain crises and compared cumulative morphine dosing in 35 children who received opioids plus paracetamol to 36 children who received opioids and placebo *(141)*. There were no significant differences in the pain scores detected at the time of disposition, and over all time intervals, or in the change of opioid use. In the paracetamol and opioids group, the mean pain score at the time of disposition was 5.5 (95% CI: 4.3–6.6) and, in the placebo group, it was 5.2 (95% CI: 4.2–6.3). No adverse events were reported. Overall, although the findings from the NRS suggest that the use of paracetamol in combination with opioids may provide potential advantages over opioids alone, the RCT did not find a significant difference in pain scores between the intervention and comparison groups.

Benefits and desirable effects

Overall, the GDG noted that there was no clinical benefit of adding paracetamol to opioids. The certainty of evidence was very low on the benefits of paracetamol and opioids compared to opioids alone for pain reduction and on the impact of paracetamol and opioids on change in opioid use, as well as hospital admission and adverse events from paracetamol and opioid use. The certainty of evidence was downgraded due to risk of bias, indirectness and imprecision for the RCT and risk of bias and imprecision for the NRS. The GDG noted that the short-term reduction of pain is more valued than the longer-term reduction of pain in patients with SCD. Pain should be controlled within 30 minutes. The GDG also noted that if pain was higher after a few hours on the paracetamol group, the benefit of taking paracetamol is small. The finding from the trial was a higher pain score *(141)*, with a mean difference of 1 point after 2 hours and more opioid use in the paracetamol group (from emergency department to hospital admission); but lower morphine use after 5 days (longer-term outcome) *(140)*.

Harms or undesirable effects

The undesirable effects were judged as moderate. The GDG noted an increase in the overall admission rate, an increase in hospitalization, and an increase in gastrointestinal and respiratory adverse events in patients receiving a combination of opioids and paracetamol.

Other considerations

Preferences, values and acceptability: The GDG judged no significant uncertainty or variability in how much people value the main outcome. Although both patients and health care providers would have valued a reduction in pain and a decrease in the consumption of opioids, and the consequent reduction in undesirable side-effects, these outcomes were not shown in the RCT. The GDG noted that, from a provider's perspective, there might be concerns regarding the number of IV medications started on infants, especially since the addition of paracetamol did not lead to a reduction of pain. Although acceptability was not assessed, there may be concerns about the use of opioids due to the risks of known adverse events. Patients and caregivers will favour the recommendation against the addition of IV paracetamol on top of opioids.

Resources required: No studies assessed costs and cost-effectiveness. The GDG judged that that the costs of IV paracetamol are high, and while oral paracetamol has negligible cost its benefit is unclear.

Equity: Paracetamol IV is not widely available in LMICs and might be costly, so using opioids against the addition of paracetamol IV should not negatively impact equity.

Feasibility: IV paracetamol may not be widely available and is costly so using opioids alone is considered to be more feasible.

Research gaps

Studies were conducted only in patients with severe pain and further research into the use of paracetamol in patients with milder to moderate pain would help determine utility for this sub-population. Studies with appropriate designs are needed on the use of paracetamol monotherapy versus combination regimens in the management of mild, moderate and severe VOC pain in children with SCD.

3.4.5 Stepwise approach to the management of acute pain in children and adolescents with SCD

Acute pain in children and adolescents with SCD is most commonly caused by VOCs. Timely initiation of analgesic therapy is critical, with the goal of beginning treatment within 30 minutes of arrival at the health facility. The choice and dose of analgesia should be guided by the patient's recent use of pain medications, the location and intensity of the pain, associated symptoms and previous responses to treatment. At home, patients often start using paracetamol or NSAIDs. If pain persists and outpatient care is sought, the severity of pain should be assessed to guide further management.

In clinical practice, analgesic selection is influenced by pain severity, patient preferences and the availability of medications at the point of care. For mild to moderate pain, NSAIDs alone may be sufficient. For moderate to severe pain, a combination of NSAIDs and opioids is suggested over opioids alone, based on evidence of improved pain control and reduced hospitalization. In cases where only one class of analgesic is available, treatment should begin with the available option, regardless of pain severity. If neither NSAIDs nor opioids are accessible, IV paracetamol may be used initially, with transition to oral formulations as appropriate.

To harmonize the recommendations into best clinical practice, the GDG proposed a cascade for acute pain management in children with SCD (Box 1).

Box 1 Best clinical practice cascade for acute pain management in children with SCD

1. Initiate NSAIDs alone for mild to moderate acute pain.
2. Reassess every 15–30 minutes; if pain is not adequately controlled within 30 minutes, add opioids.
3. For moderate to severe acute pain, begin with a combination of NSAIDs and opioids.
4. Continue reassessment every 15–30 minutes, and taper opioids as pain subsides.
5. If only NSAIDs or opioids are available, initiate treatment with the available agent.
6. If neither NSAIDs or opioids are available, begin with IV paracetamol if accessible, and switch to oral as needed.

Remarks

- Diclofenac and ibuprofen are the most commonly used NSAIDs in children with SCD.
- For moderate pain, weaker opioids such as codeine may be sufficient.
- For severe pain, strong opioids such as morphine, or alternatives like levorphanol, methadone, oxymorphone or fentanyl should be considered.
- The pain should be re-assessed every 15–30 minutes, and opioids re-administered if necessary, until adequate control of pain is achieved.
- If severe pain persists, the opioids dose may be increased incrementally to avoid central nervous system depression.
- Nonpharmacological interventions, such as distraction, local heat application, massage and positioning, may provide additional relief and should be considered as part of a comprehensive pain management strategy.

Implementation considerations

- While acute pain in children and adolescents with SCD is most commonly due to VOCs, clinicians should always evaluate the underlying cause of pain, as it may occasionally arise from other etiologies. As pain begins to resolve, opioid doses should be tapered gradually rather than abruptly stopped to avoid withdrawal symptoms, which may mimic VOC-related pain and complicate clinical assessment.
- When opioids are used, their side-effects, particularly those affecting respiratory function and sedation, should be closely monitored and preventive or supportive measures should be implemented as needed. Given that children with SCD often have poor venous access, subcutaneous administration may be preferred over IV routes. Where feasible, continuous infusion is recommended to avoid repeated injections and to provide more consistent pain control.
- Patient-controlled analgesia may be considered in settings where it is available as it allows for a constant background infusion rate and enables patients to self-administer booster doses, improving autonomy and responsiveness to pain fluctuations.

3.4.6 Blood transfusion therapy for the treatment of recurrent acute pain

Background

RBC transfusion therapy plays an important role in alleviating or preventing morbidity and mortality in patients with SCD *(142, 143)*. Indications for RBC transfusion include the correction of anaemia, management of ACS and preoperative management, and chronic transfusion for the prevention of primary and secondary stroke or silent cerebral infarction (SCI). A major goal of regular chronic RBC transfusion therapy is to maintain the HbS percentage below a target threshold to reduce SCD complications by decreasing the circulating sickle RBCs *(120)*. However, regular transfusions to manage SCD are costly, time intensive and are not without their complications, including iron overload, alloimmunization and blood-transmitted infections *(144-146)*. Excess systemic iron overload can lead to the accumulation of iron in the heart, liver, spleen and other tissues, resulting in a wide array of complications such as endocrinopathies, cardiomyopathy and hepatic failure. To prevent these complications, iron chelation therapy is essential *(129)*. Therefore, regular (chronic) RBC transfusion therapy for uncomplicated VOCs remains controversial, as its effect on the course of hospitalization or duration of painful VOC episodes has not been shown *(142, 147)*. Thus, chronic transfusion is a common treatment to reduce the incidence of painful VOC episodes. However, there are existing alternatives for SCD pain management including, but not limited to, NSAIDs and opioids. The GDG determined that there was a need to provide guidance on the role of regular chronic blood transfusions in the management of recurrent acute episodes of pain, particularly in LMICs.

Recommendation 8:

In children and adolescents (aged 0–19 years) with SCD, regular (chronic) blood transfusion with iron chelation therapy is suggested for the management of recurrent pain.

Conditional recommendation, very low certainty of evidence.

Remarks

- Regular blood transfusion should be offered through shared decision-making, with access to and adherence to regular monitoring of iron overload (e.g. serum ferritin or imaging) and appropriate iron chelation therapy.
- Patients and their families should be informed of the uncertainty regarding the benefits of regular transfusion relative to its potential burdens and risks, including iron overload and alloimmunization.
- For patients who prefer to avoid transfusion-related risks, NSAIDs and opioids may be considered as alternative options for managing recurrent pain.
- Given the cumulative exposure to blood products over the lifetime in individuals with SCD, hepatitis B immunization is recommended.
- Hydroxyurea therapy may be considered as an alternative to chronic blood transfusion for reducing recurrent pain, particularly in settings where transfusion or chelation therapy is limited or unavailable.

Justification

The GDG made a conditional recommendation for the use of regular (chronic) blood transfusion with iron chelation therapy in children and adolescents with SCD experiencing recurrent pain. This was based on very low-certainty evidence suggesting a potential reduction in pain episodes, outpatient visits and hospitalizations, which may contribute to improved quality of life. While the potential benefits were considered moderate, the GDG also acknowledged moderate harms, burdens and costs associated with chronic transfusion, including iron overload, alloimmunization and the need for long-term chelation therapy. Additionally, the resource requirements for establishing and maintaining a transfusion service, particularly in low-resource settings, may be substantial.

Despite these limitations, the overall balance of effects was judged to favour chronic transfusion in selected patients, particularly when implemented with appropriate monitoring and in the context of shared decision-making. The conditional nature of the recommendation reflects both the limited evidence of efficacy and the moderate certainty of harms.

Summary of evidence

The systematic review identified three studies conducted in the USA that assessed the role of blood transfusion and acute pain in children and adolescents with SCD: one multicentre RCT and two retrospective studies *(125, 126, 148)*. The three studies enrolled 161 children and adolescents: 130 in the RCT and 31 in the retrospective studies. Evidence was of very low certainty because of the risk of bias and imprecision. The RCT enrolled children with other indications for transfusion (silent stroke, stroke, abnormal TCD ultrasound) *(126)*. The two NRSs that included a good proportion of children with recurrent acute pain at entry were small (13–17 participants) and compared rates of painful events before and after the start of transfusions *(125, 148)*. A meta-analysis was not possible due to different outcomes and study designs.

In the RCT, hospitalization rates for pain (n = 129) were 16.2 per 100 patient-years in the chronic transfusion group and 27.6 per 100 patient-years in the observed group; however, this difference was not statistically significant *(126)*. In the NRS, the oral morphine equivalents prescribed for patients prior to and during 1 year of transfusion therapy were similar (2400 vs 2636 oral morphine equivalents/year). The total number of emergency department visits for pain was 6.0 compared to 2.5 pain visits per year, the mean hospitalizations for pain per year were 3.4 admissions compared to 0.9 admissions and the mean hospital days per year for pain crises were 23.5 days versus 4.5 days per year before and after transfusion, respectively (n = 14) *(148)*. The mean ferritin level in all 14 patients after 12 months of transfusion therapy was 1343 ng/mL (SD: 610 ng/mL) and the mean liver iron concentration for the eight patients who underwent imaging was 4.3 mg/g of dry tissue (SD: 2.5 mg/g of dry tissue). In the second study, VOC hospitalizations per year decreased from 150 hospitalizations before transfusion to five hospitalizations after transfusion (n = 17) *(125)*. All 17 patients continuing the transfusion programme had evidence of iron overload and received iron chelation therapy.

Overall, the findings suggest that regular blood transfusion may reduce pain, as well as pain-induced inpatient and outpatient visits and hospital length of stay; however, the evidence was very uncertain for all outcomes except for hospitalization rates for pain from the included RCT (low certainty of evidence). Despite the positive effects of transfusion, there is some evidence of transfusion-related complications such as iron overloading and alloimmunization.

Benefits and desirable effects

The GDG determined that the potential benefits of chronic transfusion for recurrent pain are moderate, driven by the critical outcome of pain reduction and a decrease in outpatient visits and hospitalization, and, hence, improved quality of life. The number of patients with pain was reduced by 22 per 1000 (95% CI: 122–163) and hospitalizations were lower in the transfused group (16.2 vs 27.6 per 100 patient-years). There was also a decrease in outpatient visits (6.0 vs 2.5 visits per year) and in mean hospital days for pain (23.5 days vs 4.5 days) before and after transfusion *(126)*. Overall, the findings suggest that regular blood transfusion may reduce pain, the number of pain-induced inpatient and outpatient visits and hospital length of stay. However, blood transfusion carries risks, many of which are greater in individuals with SCD than in the general population. The approach to transfusion must balance these benefits and risks, both in the decisions on when to transfuse and in the practical aspects of how transfusions are administered.

Harms and undesirable effects

The GDG judged that the undesirable effects were moderate. This decision was driven by the two documented adverse events: iron overload requiring chelation therapy and alloimmunization causing transfusion reactions. The GDG also discussed the increase in clinic visits for monthly transfusion or iron chelation therapy (4–13 clinic visits per year, $P = 0.0001$). Securing IV access also has a moderate risk of harm and pose a very high burden to patients and the health system, requiring significant time, skilled personnel and equipment and, hence, incurring moderately higher costs to deliver these therapies.

Other considerations

Preferences, values and acceptability: The GDG noted that no significant uncertainty or variability is expected in how much people value pain reduction in SCD. Families are likely to prioritize reduction in recurrent pain in patients with SCD. However, this will be influenced by other important factors such as facility access, cost, cultural and religious beliefs and school absenteeism. Patients with religious beliefs opposing blood transfusion might be opposed to the intervention. In addition, patients in settings where there are concerns about the safety of blood transfusions might be more reluctant to receive the treatment.

In most LMICs, there will be specific considerations for this intervention, such as safety concerns, the possibility of insufficient numbers of blood banks and blood shortages, lack of equipment and the cost of transfusions and iron chelation therapy, demands on the health system from necessary monthly visits, skilled personnel and the high costs of setting up a transfusion service de novo at a primary health care level. However, the GDG agreed that blood transfusion is probably acceptable to children with SCD, their caregivers, health care providers and other stakeholders because the intervention is available for multiple indications.

Resources required: There was no systematic appraisal of the resources required. However, the GDG noted that chronic transfusion therapy in patients with SCD has been associated with a significant financial impact on individuals as well as health systems, especially in LMICs. In one study conducted in Malawi, the cost of a unit of transfusion-ready blood, inclusive of safe collection and screening tests, was US$ 16.28 *(149)*. The direct costs include blood testing, donor collection, iron overload monitoring, iron chelation therapy and health personnel training. The GDG considered the direct cost of the intervention to be moderate, but it could be moderate to large for the individual patient or for setting up and maintaining a transfusion service at the primary care level.

Equity: Recommending chronic blood transfusion may unintentionally create inequities, especially in settings where patients face high out-of-pocket costs and health systems are under resourced, with limited transfusion services and concerns about blood safety. The GDG also noted that, in some instances, access to transfusion might be challenging, and regular chronic transfusion may strain the health system, leading to more inequities affecting other populations in need of blood services. Until the system is ready to make changes, extra efforts will be required to make the recommendation equitable.

Feasibility: Blood transfusion is widely available in many hospitals, even in LMICs, and should be feasible to implement, but where hospitals are not available, transfusion services may not be feasible. The GDG noted that the feasibility of the intervention will most likely be variable depending on the availability of blood transfusion services and the required implementation resources. The GDG also discussed implementation considerations and the impact of the recommendations on health systems, especially given that it will drive demand for iron chelation therapy and can help promote policy changes to make iron chelators more available.

Implementation considerations

- Regular blood transfusions without monitoring for iron overload and giving iron chelation therapy can be very dangerous. The GDG emphasized that implementation of regular blood transfusion must be accompanied by monitoring for iron overload using blood tests (serum ferritin), liver biopsy or imaging and the subsequent initiation of appropriate iron chelation with oral (deferasirox or deferiprone) or subcutaneous/IV (deferoxamine) agents, if required.

Research gaps

The recommendation for regular blood transfusion with iron chelation therapy for recurrent pain in children and adolescents with SCD is based on very limited and low-certainty evidence. To strengthen the evidence base and guide future clinical and policy decisions, the following research priorities were identified.

- RCTs comparing regular blood transfusion with non-transfusion regimens (e.g. hydroxyurea, NSAIDs or opioids) for the management of recurrent pain in children and adolescents with SCD.
- Studies are needed to determine when transfusion should be initiated during recurrent pain episodes and how frequently it should be administered to achieve optimal outcomes.
- Further research is required to quantify the short- and long-term risks and benefits of chronic transfusion, including its impact on pain frequency, quality of life and complications such as iron overload and alloimmunization.
- Studies should evaluate the role of other treatment options, such as hydroxyurea, nitric oxide and stem cell transplantation, either alone or in combination with transfusion, for managing recurrent pain.
- Evidence is needed on the effectiveness of chronic transfusion for pain management across different SCD genotypes, particularly those with more severe clinical manifestations (e.g. HbS/Sβ^0 thalassaemia).
- Research should assess the feasibility, acceptability and cost-effectiveness of chronic transfusion programmes in low-resource settings, including strategies for monitoring iron overload and ensuring access to chelation therapy.

3.5 Antibiotics and blood transfusion in the management of ACS

3.5.1 Background

ACS is a serious condition that carries a high rate of morbidity and is a leading cause of death in patients with SCD. Approximately 50% of patients with SCD will experience an ACS episode, with peak incidence occurring in children between the ages of 2 and 4 years. Overall, ACS accounts for approximately 25% of deaths in patients with SCD *(150, 151)*. ACS is a VOC of the pulmonary vasculature that results in the deoxygenation of haemoglobin and the sickling of erythrocytes, which can cause further vaso-occlusion, ischaemia and endothelial injury *(152-155)*. It is indistinguishable from pneumonia and typically presents as chest pain, cough, dyspnoea, fever and/or leukocytosis *(156, 157)*. ACS is one of the common causes of hospitalization in patients with SCD, and severe ACS can present with rapid respiratory compromise and multiorgan failure *(158)*. The diagnosis of ACS is based on clinical symptoms and radiographic findings, a new segmental radiodensity on chest imaging, and one of the following: 1) fever (38.5°C); 2) hypoxaemia (>2% decrease in peripheral oxygen saturation (SpO_2) or PaO_2 <60 mmHg); 3) tachypnoea; and 4) cough, chest pain, rales, wheezes *(150, 159)*.

ACS most commonly occurs 1–3 days after the onset of pain, and is typically triggered by a VOC event *(150)*. The triggers of vaso-occlusion may be infectious or non-infectious, although up to 46% of cases have no identified cause *(150, 160)*. In children, among those cases with identifiable causes, about 40% are frequently associated with pulmonary infections (bacterial or viral). The most frequently encountered infectious causes are mycoplasma, Chlamydia, respiratory syncytial virus and parvovirus *(150)*. Pulmonary infarction and fat embolism are also significant contributors to ACS in children *(161)*. Early recognition and prompt initiation of treatment have been associated with lower mortality rates, shorter hospital stays, decreased health care costs and a reduced likelihood of recurrence *(162, 163)*. Once initiated, treatment of ACS should be aggressive due to the potential rapid progression of the disease *(164)*.

Current management of ACS involves close monitoring of vital signs, pain control, IV fluids, antibiotics, supplemental oxygen and blood transfusions *(163, 165, 166)*. Pain control typically begins with NSAIDs but can be quickly accelerated to opioids as optimal pain control is important for full respiratory effort. Fluid management in cases of dehydration, such as hypovolaemia, can exacerbate sickling; however, fluid overload should be avoided *(167)*. Broad-spectrum antibiotics are administered to every patient with ACS because the risk of community-acquired pneumonia is higher in the paediatric population and is difficult to distinguish from pneumonia *(168-170)*. Coverage for atypical organisms is necessary as they are also common causes of pneumonia in patients with SCD *(171, 172)*. Supplemental oxygen is administered to correct low oxygen saturation (SpO_2) or arterial partial pressure of oxygen (PaO_2) in patients *(173)*. In addition, packed RBC transfusions are used to increase the blood's oxygen-carrying capacity and reduce complications of VOC by reducing the percentage of HbS, though there is a paucity of high-quality data *(120, 174-177)*. However, despite many guidelines recommending the use of antibiotics and blood transfusion for treating symptomatic ACS in patients with SCD, they remain controversial *(168, 170)*.

3.5.2 Antibiotic therapy in the treatment of ACS

Recommendation 9:

In children and adolescents (aged 0–19 years) with SCD and a clinical diagnosis of ACS, the use of antibiotics in addition to standard therapeutic and supportive interventions is suggested.

Conditional recommendation, low certainty of evidence.

Remarks

- Empirical broad-spectrum antibiotic therapy should include a third-generation cephalosporin to cover common Gram-negative and Gram-positive organisms, along with a macrolide to target atypical bacteria such as Mycoplasma pneumoniae and Chlamydia pneumoniae.
- Where available, local bacterial prevalence and antimicrobial susceptibility patterns should guide the choice of specific antibiotics.
- In children, distinguishing ACS from pneumonia can be challenging due to overlapping clinical features. Infectious causes are more likely to be implicated in children than in adults.
- In cases of cephalosporin allergy, appropriate antibiotic alternatives should be considered based on local guidelines and susceptibility data.
- Standard therapeutic and supportive interventions for ACS include pain management, IV fluids, oxygen supplementation, blood transfusion or exchange transfusion, and respiratory support, as clinically indicated.

Justification

The GDG made a conditional recommendation in favour of adding antibiotics to standard care for children and adolescents with SCD and a clinical diagnosis of ACS. This decision was based on low-certainty evidence suggesting moderate desirable effects, particularly the reduction in 30-day readmission rates. The GDG also considered the short duration of antibiotic use and the relatively low likelihood of serious adverse effects. ACS is a leading cause of hospitalization, and the most common cause of morbidity and mortality in this population. Although ACS can result from multiple pathophysiological mechanisms, infectious causes are a major contributor, especially in children, and cannot reliably be distinguished from pneumonia based on clinical presentation alone.

Given the potential for rapid progression and the critical importance of early intervention, the GDG judged that the benefits of empirical antibiotic therapy outweigh the potential harms, thereby supporting a conditional recommendation.

Summary of evidence

The systematic review identified only two NRS studies, which were conducted in the USA *(169, 178)*. One retrospective study, involving 7178 children, reported on 7- and 30-day rehospitalization rates due to ACS, mortality and length of stay for combination therapy (cephalosporin + macrolide), cephalosporin alone and macrolide alone versus neither antibiotic therapy *(169)*. The other study, involving 8856 children, assessed the association of antibiotic choice with 30-day rehospitalization, length of stay and mortality in patients with SCD and ACS *(178)*. Both studies used the same data source, and there was considerable overlap between the patients and hospitalizations recorded in each study. Neither study reported on the resolution of signs and adverse events.

The review showed that antibiotic treatment was associated with fewer ACS-related 30-day rehospitalizations compared with no antibiotic combination therapy. Combination therapy was associated with the greatest reduction (RR 0.19; 95% CI 0.17–0.20), corresponding to approximately 220 fewer rehospitalizations per 1000 children treated compared with no combination therapy. Cephalosporin therapy alone was also associated with fewer rehospitalizations (RR 0.25; 95% CI 0.23–0.27), equivalent to about 205 fewer per 1000, while macrolide therapy alone showed a similar reduction (RR 0.22; 95% CI 0.19–0.23), corresponding to around 215 fewer rehospitalizations per 1000 compared with no combination therapy *(169)*. There was a much smaller impact on 7-day hospitalization, which varied by type of treatment and on mortality. Overall, there is low certainty of evidence that antibiotics may be useful for the treatment of children with ACS and SCD, but it was not possible to determine whether treatment with either cephalosporins, macrolides or a combination of these treatments could reduce mortality due to the limited number of deaths observed. Overall, the evidence was assessed to be of low to very low certainty, largely driven by a single NRS for each outcome, the inclusion of populations with diagnoses of ACS or pneumonia and potential confounding factors.

Benefits and desirable effects

The benefits were judged as moderate. This was driven by the fact that cephalosporins, macrolides and different combinations of these therapies were effective in reducing 30-day readmissions for patients who were initially hospitalized due to acute ACS. In addition, it is challenging to make an accurate diagnosis of ACS and differentiate it from pneumonia, particularly in LMICs where there may be limited facilities. Given the high incidence of ACS in children with SCD (25.3 per 100 patient-years), rapid progress and the high mortality associated with ACS, empirical antibiotics are more likely to be beneficial. The GDG also considered that in practice, as infection is a major cause of ACS, any SCD child with fever is empirically put on antibiotics even though the trigger may not be an infection.

Harms and undesirable effects

The included studies did not report any adverse events. However, the GDG judged the undesirable anticipated effects as small. This was driven by the fact that the antibiotics included have been used relatively extensively in clinical practice, have known, low-risk adverse effects and are administered for a short duration with less likelihood of antimicrobial resistance. However, the GDG noted that macrolides may have additional drug interactions with other medications and emphasized the importance of the judicious use of a broad-spectrum combination of cephalosporins with macrolides in hospitalized patients in the context of antimicrobial resistance and stewardship.

Other considerations

Preferences, values and acceptability: The GDG determined that there was probably no important uncertainty or variability as patients, parents, caregivers and health care workers are less likely to oppose antibiotics in children with SCD with ACS. However, in the case of combination parenteral antibiotics, some people may be disadvantaged because of high cost or unavailability. Patients would not be opposed to receiving antibiotic treatment. The GDG determined that the antibiotic intervention would be acceptable for children with SCD, their caregivers, their clinical care providers and other stakeholders because it is relatively inexpensive, readily available and has been shown to reduce hospital readmissions.

Resources required: The systematic review did not identify any studies that looked at cost or cost-effectiveness of the role of antibiotics in children with ACS. For the treatment of ACS, the recommended combination of antibiotics, injectable cephalosporins and macrolides are generally available in LMICs. The cost estimations are: ceftriaxone IM, US$ 2–3 per vial; cefuroxime, US$ 3; and azithromycin, US$ 3–5 *(179)*. Given that ACS is a serious complication among children with SCD, the GDG determined the cost requirements as moderate compared to the costs of hospitalization and hospital stays due to SCD complications.

Equity: Some people may be disadvantaged by the cost and availability of the parenteral antibiotics, particularly in rural areas. The recommendation could be a burden on these families and hospitals, thereby impacting equity.

Feasibility: The GDG determined that the intervention is feasible because antibiotic treatment for ACS or pneumonia is widely practiced. In addition, there is extensive experience in the use of antibiotics for children with SCD as part of national disease management programmes.

Implementation considerations

- For some countries, particularly in LMICs, national screening programmes are less established, and there may be barriers to accessing regular treatment that limit implementation.

Research gaps

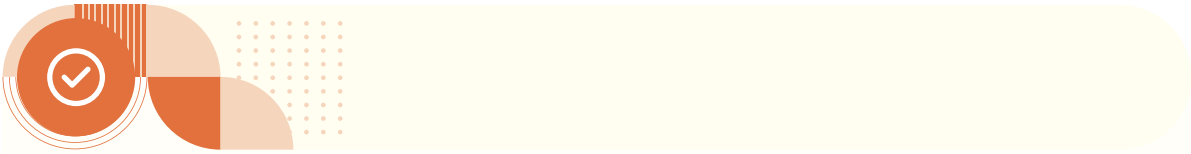
There is a significant lack of high-quality evidence on the use of antibiotics for the treatment of ACS in children and adolescents with SCD. The current recommendation is based on limited data, and further research is needed to guide optimal antibiotic use in this population. The following research priorities were identified.

- Studies are needed to evaluate the effectiveness of different antibiotics – alone or in combination – for the treatment of paediatric ACS. These studies should assess clinical outcomes such as symptom resolution, hospital length of stay, readmission rates and mortality.
- Comparative studies should explore the use of broad-spectrum versus narrow-spectrum antibiotics, optimal treatment durations and the impact of antimicrobial resistance on treatment outcomes.
- Contextual and implementation research is needed to assess the acceptability, feasibility, cost-effectiveness and equity of antibiotic use for ACS in various health system settings, particularly in LMICs.
- Implementation research is needed to identify the barriers and facilitators to timely antibiotic administration during ACS episodes and evaluate strategies to improve uptake and adherence to treatment protocols.

3.5.3 Blood transfusion therapy in the management of ACS

Background

Blood transfusion is an integral component in the management of ACS *(120, 175)*. Transfusion is said to improve the oxygen-carrying capacity of the blood and to lower the risk of disease progression *(174, 176)*. For patients with hypoxaemia, simple blood transfusions or RBC exchange transfusions may be performed to increase oxygen-carrying capacity. Patients hospitalized with ACS are often considered for transfusion, with the goal of a haemoglobin level of 10 g/dL or haematocrit 30%. However, patients with haemoglobin levels >9 g/dL and no hypoxaemia may not require transfusion *(177, 180)*. Those with haemoglobin levels >11 g/dL are not recommended for transfusion due to increased viscosity and further vaso-occlusion. In severe cases of ACS, such as severe hypoxaemia, the presence of multilobar disease on chest radiographs or failure of improvement with simple blood transfusion, exchange transfusions are considered *(174, 180)*. Although it appears that blood transfusion may play a role in the management of ACS in people with SCD, and may be a widely accepted clinical practice, there is no reliable evidence to support or refute this perceived role *(170, 175)*.



Recommendation 10:

In children and adolescents (aged 0–19 years) with SCD and a clinical diagnosis of ACS, blood transfusion in combination with standard therapeutic interventions is suggested rather than standard therapeutic interventions alone.

Conditional recommendation, very low certainty of evidence.

Remarks

- Blood transfusion may improve oxygenation, which is a critical outcome in children with ACS, particularly in the presence of hypoxaemia and anaemia where a dose–response effect may be observed.
- The decision to initiate transfusion should be guided by the severity of ACS symptoms, including the presence of severe hypoxaemia, severe anaemia, stroke or clinical deterioration.
- In patients without hypoxaemia or a significant drop in haemoglobin, the potential risks of blood transfusion (e.g. alloimmunization, iron overload, transfusion reactions) may outweigh the uncertain benefits, and some patients may reasonably choose to decline transfusion.
- Shared decision-making with patients and caregivers is essential, taking into account clinical presentation, transfusion risks and patient values and preferences.

Justification

ACS is a potentially life-threatening pulmonary complication in children and adolescents with SCD, typically resulting from vaso-occlusion in the pulmonary microvasculature. This leads to local tissue infarction, hypoxia and inflammation. Blood transfusion aims to increase oxygen-carrying capacity and reduce the proportion of HbS by diluting it with normal haemoglobin (HbA), thereby mitigating further vaso-occlusion and improving tissue oxygenation.

Although the certainty of the evidence was very low, the GDG considered the potential benefits of transfusion, including reduced episodes of ACS, lower hospitalization rates, shorter lengths of stay and improved oxygenation, to be clinically meaningful. The GDG also acknowledged the physiological rationale for transfusion, particularly the role of HbA-containing RBCs in improving oxygen delivery without promoting sickling. However, the potential risks of transfusion, such as iron overload, alloimmunization and resource demands, must be carefully weighed up. In the absence of other indications, transfusion should be administered cautiously, with decisions guided by clinical severity and patient preferences. The conditional recommendation reflects the limited evidence base and the need for individualized, context-sensitive implementation.

Summary of evidence

The systematic review identified three relevant NRSs that assessed the role of blood transfusion compared to standard therapy in patients with SCD with suspected ACS *(178, 181, 182)*. One prospective study analysed the effects of transfusion on the clinical course and oxygenation of children with SCD and ACS *(181)*. Another retrospective study assessed the effects of chronic transfusion on the prevention of new episodes of ACS in children with SCD with recurrent or unusually severe ACS *(182)*. The third NRS is a large retrospective study that assessed the association of antibiotic choice on the length of hospital stay and readmission rates in patients with SCD and ACS *(178)*. The critical outcomes were incidence of recurrent ACS, 30-day ACS-related hospital readmission, hospital length of stay for ACS and PaO_2. ACS was assessed through recurrent ACS incidence rate (very low certainty of evidence) and 30-day ACS-related hospital readmissions (very low certainty of evidence). In the retrospective study, the ACS incidence was 1.3 episodes per patient-year before treatment; during treatment, it decreased to 0.1 episodes per patient-year (study sample size: 27 participants) *(182)*. In the large retrospective study, the administration of at least one packed RBC transfusion was associated with decreased ACS-related 30-day hospital readmission (OR: 0.60; 95% CI: 0.43–0.83) *(178)*.

Two studies reported on hospital length of stay. In the prospective study of 36 patients with more severe disease at presentation, the mean length of stay in patients who received transfusion was 7.4 days (SD: 3.2) versus 6.9 days (SD: 3.3) in those who did not have a transfusion *(181)*. In the retrospective study, the median length of stay was 5 days (range: 3–15) before chronic transfusion and 3 days (range: 2–7) during therapy (n = 27) *(182)*. The partial pressure of oxygen in participants while breathing room air, assessed 4–12 hours before and 12–24 hours after transfusion, showed a significant mean difference of 21 mmHg higher (range: 8.95–33.05) after transfusion *(181)*. Overall, the studies showed significant reductions in recurrent episodes of ACS, ACS-related 30-day readmission rates, changes in all indexes of oxygenation and improved haemoglobin levels with blood transfusion when compared to standard care and pretreatment or no RBC transfusion.

Benefits and desirable effects

The GDG judged that blood transfusion may have potential benefits in reducing episodes of ACS and ACS-related hospital readmission and length of stay and in increasing oxygenation, although the certainty of evidence was very low. This was driven by the consideration that blood transfusion and other supportive care decreased the incidence of ACS to 0.1 episodes per patient per year, and reduced ACS 30-day hospital readmission rates and hospital stays. Improvement in oxygenation was also considered to be a critical outcome since oxygen saturation/hypoxia is used to monitor patients with ACS. In addition, transfusion may prevent harm, especially in children with SCD and ACS with low haemoglobin or hypoxaemia, and transfusion in these patients may have a dose–response effect. This also takes into consideration that more severe ACS is commonly accompanied with severe hypoxaemia, severe anaemia, or even stroke. However, the GDG noted that a decrease in hospitalization could be due to several other confounding factors and may not be a driver of the benefit.

Harms and undesirable effects

The GDG noted that the studies in the systematic review did not report any adverse events of transfusion in the acute setting, but determined that the undesirable effects are variable. There may be an increased risk from blood transfusion in the SCD population because they may have had multiple transfusions in the past. The potential harms of blood transfusion depend on co-existing clinical indications like severe anaemia, stroke, or hypoxaemia, the patient's prior transfusion history, and the overall risk–benefit balance associated with repeated transfusions.

The GDG recognized that although the reviewed studies did not report adverse events, there are known adverse events, such as blood transfusion reactions, alloimmunization, acute neurological events and bloodborne infections, following transfusion in patients with ACS *(183)*. Patients with SCD who have history of recurrent blood transfusion are at increased risk of developing red cell alloantibodies and subsequently developing an immunological transfusion reaction. Given that ACS is a significantly inflammatory condition, transfusions during this pro-inflammatory state may induce higher rates of alloimmunization and hyperviscosity and therefore should be used cautiously balancing the risk–benefit ratio. For example, simple transfusion in patients with higher haemoglobin (9.0 g/dL or more) may lead to hyperviscosity and worsening of sickling.

Other considerations

Preferences, values and acceptability: The GDG determined that the values will be uncertain or variable depending on the context. These will depend on the cost of the treatment, cultural and religious factors, and proximity to health facilities. There may also be issues with lack of expertise in local health facilities and insufficient blood banks. Patients in settings with concerns about the safety of blood, or those with religious beliefs opposing blood transfusion, might be opposed or reluctant to receive blood transfusions. However, blood transfusion is likely to be acceptable to children with SCD, their caregivers, health care providers and other stakeholders because of its multiple indications. However, it is important to take into consideration religious preferences, blood safety concerns, cost and the severity of ACS presentation.

Resources required: The GDG recognized the lack of included studies on cost, but considered the cost to be significant. Overburdened health systems with inadequate blood transfusion services with poor blood safety may be disadvantaged by a recommendation for transfusion *(13)*. Although blood transfusion in most LMICs is generally provided by the government, the blood transfusion system (collection of blood, safe keeping and delivery) does incur costs, and families will face additional costs for related factors, such as travel and hospitalization *(149)*. However, fewer readmissions and lower recurrent ACS rates may indicate a degree of cost-effectiveness of transfusion in addition to standard therapeutic interventions that favour the intervention *(184)*.

Equity: The GDG judged the impact on equity as variable. Blood transfusion requires a hospital stay, meaning that those who cannot access hospital care might be disadvantaged by this recommendation. Hospital admission and its impact on school absenteeism will disadvantage those living in rural settings. Other populations who need transfusion for other reasons, such as children with severe malaria or anaemia, may be disadvantaged because of this recommendation. In addition, the level of the health facility, the capacity of the blood transfusion system, the availability of safe blood and the financial costs can be barriers to the high-quality provision of this intervention, whether in rural or urban settings.

Feasibility: The GDG determined that implementation is probably feasible. This was driven by the consideration of the wide availability of blood transfusion in many hospitals in LMICs and its use for other clinical indications. However, shortages of blood, limited resources and the need for red cell phenotyping and antibody identification remain major challenges in many LMICs. Vascular access, which requires skilled personnel, is an important consideration in cases where peripheral access may not be possible, and central venous catheters may be necessary for adequate access over time. In addition, adequate RBC antigen matching to mitigate the risk of RBC alloimmunization, which patients with SCD are at risk of developing, may need additional resources.

Implementation considerations

- Children and adolescents with SCD should be immunized against hepatitis B because they have a higher lifetime chance of receiving repeated blood transfusion, which carries an increased risk of this disease.
- In malaria endemic areas, chemoprophylaxis after a blood transfusion is also recommended.

Research gaps

The evidence supporting the use of blood transfusion for ACS in children and adolescents with SCD is limited to NRSs, all of which were conducted in high-income countries, primarily the USA. As a result, the certainty of evidence is very low, and conclusions regarding the effectiveness of transfusion in this context remain uncertain. There is a critical need for high-quality research, including RCTs, to evaluate the role of blood transfusion in the management of ACS across diverse settings. Key research questions identified include the following.

- What is the optimal timing for initiating blood transfusion during an ACS episode to maximize clinical benefit?
- What are the short- and long-term risks and benefits of blood transfusion in children and adolescents with ACS?
- What is the role of chronic transfusion for recurrent ACS in comparison to alternative therapies such as hydroxyurea, nitric oxide or stem cell transplantation?
- How does the effectiveness of blood transfusion vary across different SCD genotypes, particularly those associated with more severe clinical manifestations (e.g. HbS/β^0-thalassemia)?

Additionally, studies conducted in LMICs are needed to assess the feasibility, safety and impact of transfusion strategies in resource-limited settings.

3.6 Prevention and treatment of stroke in children with SCD

3.6.1 Background

The predominant neurological manifestations of SCD include ischaemic and haemorrhagic stroke, SCIs, chronic headaches, epilepsy and cognitive impairment *(185, 186)*. Stroke and other complications of cerebrovascular disease represent significant morbidity and mortality for children with SCD. Approximately 11% of SCD patients have a stroke by the age of 19 years, with the risk being highest during the first decade, and most significant between the ages of 2 and 5 years *(187)*. Stroke and cerebrovascular complications result from haemolysis, vaso-occlusion and inflammation, which alter cerebral blood flow and promote vasculopathy, often causing ischaemic strokes or haemorrhagic strokes *(187, 188)*. Ischaemic strokes typically result from cerebral artery narrowing, while haemorrhagic stroke is associated with vessel rupture *(188)*.

Ischaemic strokes are characterized by slurred speech, weakness in limbs, seizures, coma and cognitive impairments, but the most common presentation is acute hemiplegia. Haemolysis contributes to vascular dysfunction, while inflammation promotes cerebrovascular complications *(109, 189, 190)*. The differentiation between ischaemic and haemorrhagic stroke in patients with SCD is crucial for effective management, which may include blood transfusion therapy and/or anticoagulation *(188, 191-193)*. Recurrent or secondary strokes occur in half to two thirds of untreated individuals and are associated with increasing morbidity and mortality *(187)*. Beyond the immediate stroke risks, neurocognitive and psychological complications also occur, necessitating screening and interventions to prevent life-threatening complications and enhance quality of life.

Acute stroke is one of the common medical emergencies in children with SCD, particularly where primary stroke prevention is not standard care. Timely response is required to minimize further ischaemic brain injury. Hence, it is common practice to treat with prompt blood transfusion, anticoagulants and sometimes surgery, while chronic regular blood transfusions and hydroxyurea are commonly used to prevent primary or secondary stroke *(8, 143, 177, 192, 194)*. Without secondary stroke prevention, more than half of patients who experience a first episode will have a recurrence *(195)*. Observational studies have established that chronic simple or exchange blood transfusions decrease the risk of a new stroke *(123, 174, 196)*. For children with HbSS or HbSβ^0-thalassemia and a history of prior stroke, most guidelines recommend blood transfusion goals for secondary stroke prevention of a haemoglobin level above 9 g/dL at all times and maintaining the HbS level at <30% of total haemoglobin until the time of the next transfusion *(120)*. However, even with optimal management, chronic regular blood transfusions are commonly complicated by alloimmunization, autoimmune haemolysis, iron overload, infections or noncompliance *(197-199)*. Although exchange transfusion mitigates iron overload, it is more demanding and requires technical expertise, and more units of blood, which further increases the risk of alloimmunization. Therefore, despite these current treatment and preventive measures for stroke, knowledge gaps remain regarding the best choices and modes of treatment *(8)*.

3.6.2 Exchange blood transfusion in the management of suspected acute symptomatic stroke

Recommendation 11:

In children and adolescents (aged 0–19 years) with SCD and suspected acute symptomatic stroke, exchange transfusion is suggested rather than simple RBC transfusion.

Conditional recommendation, very low certainty of evidence.

Remarks

- All children with suspected acute symptomatic stroke should receive prompt blood transfusion. Where exchange transfusion is not feasible or is delayed, simple RBC transfusion is an acceptable alternative.
- Simple transfusion should be administered with caution to avoid excessive increases in post-transfusion haemoglobin concentration, which may increase blood viscosity and worsen clinical outcomes.
- The choice between exchange and simple RBC transfusion should be guided by clinical urgency, local resource availability and the potential for improved outcomes with exchange transfusion, particularly in situations where rapid reduction of haemoglobin S is critical.

Justification

Acute stroke is a serious and time-sensitive complication in children and adolescents with SCD, requiring immediate intervention to minimize further ischaemic injury and prevent long-term neurological sequelae. The GDG based this recommendation on very low-certainty evidence from a single retrospective observational study comparing exchange transfusion to simple transfusion in the acute management of ischaemic stroke. Despite the limited evidence base, the GDG recognized the strong physiological rationale for exchange transfusion, which rapidly reduces the proportion of HbS while avoiding the risk of post-transfusion hyperviscosity associated with simple transfusion.

Exchange transfusion is therefore preferred when it is immediately available and feasible. However, in settings where exchange transfusion is not accessible or would result in treatment delays, simple RBC transfusion remains an acceptable and potentially life-saving alternative. The decision between transfusion modalities should be guided by clinical urgency, haemoglobin levels, the presence of neurological deficits and local transfusion capacity. The conditional nature of the recommendation reflects the limited evidence and the need for individualized decision-making based on available resources and patient-specific factors.

Summary of evidence

A systematic review identified only one NRS conducted in the USA *(196)*. This was a retrospective cohort study involving 124 children with SCA and acute ischaemic stroke. The study assessed the effectiveness of simple RBC transfusion or exchange transfusion in the treatment of acute stroke and in the prevention of secondary stroke. The mean age at first stroke was 6.3 years (range: 1.4–14 years) and the mean follow-up time was 10.1 years (range: 5–24 years). For secondary stroke prevention, patients had undergone chronic blood transfusions every 6 weeks for at least 5 years after the first stroke. Red cell exchange transfusion was the most common initial treatment for the first stroke, regardless of the duration of symptoms.

Initial transfusion treatment for acute stroke was available for 52 (65%) out of 80 patients who sought medical care within 24 hours of the onset of acute stroke symptoms. In patients initially treated with simple RBC transfusion, recurrent stroke occurred in 57% (eight out of 14 patients) compared to 21% (eight out of 38 patients) in those treated with RBC exchange transfusion. Children with SCA and first acute stroke receiving simple RBC transfusion had a 5-fold greater risk (RR: 0.37; 95% CI: 0.17–0.80) of having a second stroke in comparison to those receiving exchange transfusion. Among patients without a medical history (fever, acute anaemia, ACS or high blood pressure) prior to the acute stroke, those who received simple RBC transfusion had an 8-times greater risk of a second stroke (eight out of 11 patients) compared to patients treated with exchange transfusion (seven out of 28 patients) (RR: 8.0; 95% CI: 1.7–3.8). No transfusion-related complications or adverse events were reported *(196)*.

Overall, the study found that exchange transfusion may reduce risk of recurrent stroke when compared to simple RBC transfusion for stroke prophylaxis in paediatric SCD patients; however, the evidence is very uncertain. Exchange transfusion on a chronic basis may be further protective in the prevention of secondary stroke, when compared to chronic simple transfusion. Comparable rates of medical antecedent events were observed with the two types of transfusion, although the evidence was very uncertain.

Benefits and desirable effects

The available evidence was very indirect and had limitations, and as a result the GDG decided that the benefits were uncertain. There were concerns about the assessed outcomes because the recurrence of stroke and number of patients without a medical antecedent event were indirectly ascertained. In addition, there was a lack of clarity about whether participants were screened to ascertain if the acute stroke episode was the first episode. The GDG considered that both simple transfusion or exchange transfusion can reduce acute sickling and improve cerebral blood flow in acute stroke. Nonetheless, the GDG noted that patients who present with signs and symptoms of an acute episode of ischaemic stroke might benefit more from exchange transfusion. In addition, exchange transfusion may have more beneficial effects if the primary objective is to reduce HbS concentration without increasing blood viscosity. However, in children presenting with a focal neurological deficit suggestive of an ischaemic event and low haemoglobin, increasing the haemoglobin level with a simple transfusion is the best option to achieve the immediate goal of improving oxygen delivery to the brain.

Harms or undesirable effects

The GDG noted that, although the reviewed study did not report on adverse events, there are known complications associated with blood transfusion *(197)*. These include blood transfusion reactions, infection, alloimmunization and iron overload, which typically requires iron chelation therapy. In addition, exchange transfusion may lead to complications associated with central line placement (vascular injury, local and systemic infection, and catheter-related venous thrombosis) and haemodynamic problems (dizziness, syncope, headache, weakness and a possible risk of acute neurological complications caused by acute anaemia). However, the GDG judged that timely treatment with blood transfusion therapy for acute stroke outweighs the risk of treatment and, where available, automated exchange may have fewer haemodynamic risks, although it is more expensive.

Other considerations

Preferences, values and acceptability: Patients, families and providers will prioritize reduction of stroke in children and adolescents with SCD, and, as such, there is probably no important uncertainty or variability in how much people value the outcome. Since exchange transfusion is more beneficial than simple transfusion during an acute stroke, the GDG determined that it would be acceptable to both patients and providers. However, the preference and acceptability will be influenced by the cost of exchange transfusion, cultural factors and proximity to health facilities. There may also be issues with lack of expertise in local health facilities and insufficient blood banks.

Resources required: Resource requirements were not included in the systematic review. However, access to safe blood in LMICs, where the SCD burden is highest, is often restricted. Simple or exchange transfusion in patients with SCD may pose a significant burden on individuals and health systems. However, costs will vary depending on the blood transfusion services in the health system. Although the initial cost of equipment is high for an automated exchange transfusion, where available, it may potentially reduce the overall resources used, the disease burden, bed retention and the need for chelation therapy compared to simple transfusion *(200)*. Thus, an assessment of the availability and economic burden of sickle-cell complications that require exchange transfusions is needed in the context of settings with limited financial resources.

Equity: The GDG determined that the recommendation will more likely increase equity for patients with SCD if exchange transfusion becomes more widely available, even in LMICs. Prompt blood transfusion to prevent extension of acute stroke will decrease the magnitude of stroke-related disability and mortality in children with SCD, improving health equity. However, the high cost and the expertise required for exchange transfusion may disadvantage those who cannot access this treatment, and this is likely to reduce equity compared to simple transfusion.

Feasibility: Blood transfusion therapy is a key treatment and remains an important part of alleviating or preventing morbidity and mortality in patients with SCD with acute and chronic complications. In terms of feasibility, exchange transfusion often requires central line placement and admission to an intensive care unit, although it can also be performed in a non-ICU setting using peripheral venous access. It therefore requires clinical expertise that may not be readily available in many facilities in LMICs. Where automated exchange transfusion is not possible, manual exchange requires more staff and leads to an increased workload.

Implementation considerations

- In settings with limited resources and capacities for exchange transfusions, simple transfusion is feasible as an immediate treatment, and, where necessary, patients can be referred for further care at referral hospitals with the appropriate facilities.

Research gaps

Further research is needed to strengthen the evidence base for the management of SCD in children and adolescents, particularly in relation to acute stroke and transfusion strategies. Further studies should be conducted in both high-income countries and LMICs, with adequate control for confounding factors and inclusion of all SCD genotypes, especially those associated with more severe clinical manifestations, such as SCD-Sβ^0-thalassaemia. Studies should also aim for larger sample sizes and longer follow-up periods to improve the generalizability and robustness of findings. Specifically, the following areas warrant further research.

- Prospective RCTs directly comparing exchange transfusion with simple RBC transfusion in the acute management of paediatric stroke.
- Optimal timing transfusion, including how soon after symptom onset transfusion should be initiated and its impact on acute clinical outcomes, such as symptom resolution and neurological recovery.
- Comparative risks and benefits of different transfusion modalities, including manual versus automated exchange transfusion, and their effectiveness relative to simple transfusion.
- Economic evaluation, including cost-effectiveness, resource utilization and hospital length of stay, for health system planning and policy decisions.

3.6.3 Regular RBC transfusion versus hydroxyurea therapy in the prevention of secondary stroke

Background

Recurrent (secondary) strokes occur in about 50–75% of untreated patients *(201)*. They lead to devastating complications with lifelong sequelae, including cognitive morbidity, an increased risk of future cerebral infarcts, increasing morbidity and premature death *(195)*. Silent cerebral infarctions (SCIs), present in 17% to 27% of children with SCA, often go unnoticed and can cause significant neurological and cognitive disability. Without secondary stroke prevention, more than half of patients who experience a first episode of stroke will have a recurrence *(195)*. Chronic regular blood transfusions and hydroxyurea therapy are commonly used to prevent primary or secondary stroke in children with SCD *(8, 143, 177, 192, 194)*. Observational studies show that regular blood transfusions decrease the risk of a new stroke *(123, 174, 196)*.

However, even in the setting of optimal management, chronic blood transfusion management is complicated by alloimmunization and iron overload *(197-199)*. While exchange transfusions may mitigate iron overload, they are technically more demanding and require more units of blood, which further increases the risk of alloimmunization. Given the adverse events and challenges associated with chronic transfusion, hydroxyurea therapy has been suggested as an alternative *(202-204)*. Hydroxyurea therapy increases total haemoglobin and HbF and has been shown to decrease the frequency of SCD complications, including primary and secondary stroke, and the need for blood transfusions *(83, 205)*. However, it is not clear whether the use of hydroxyurea alone can prevent the risk of recurrent stroke.

Recommendation 12:

In children and adolescents (aged 0–19 years) with SCD at risk of recurrent stroke (e.g. history of stroke, haemoglobin S >30% and haemoglobin <9 g/dL), regular blood transfusion with iron chelation therapy is suggested rather than hydroxyurea therapy alone for secondary stroke prevention.

Conditional recommendation, very low certainty of evidence.

Remarks

- This recommendation assumes that all children and adolescents with SCA aged 9 months and older are already receiving hydroxyurea therapy as standard care. Regular blood transfusion and iron chelation are additional interventions specifically for secondary stroke prevention.
- In practice, children at risk of recurrent stroke may continue to receive hydroxyurea alongside regular blood transfusion and chelation therapy, depending on the clinical judgement and resource availability.
- The decision to initiate or continue transfusion therapy should be based on shared decision-making, considering the risks of iron overload, alloimmunization and the burden of chronic transfusion, balanced against the high risk of recurrent stroke.

Justification

The GDG made a conditional recommendation in favour of regular blood transfusion with iron chelation therapy over hydroxyurea alone for secondary stroke prevention in children and adolescents with SCD. This recommendation was based on the high risk of recurrent stroke and the associated long-term neurological and cognitive complications, which can significantly impair quality of life. Although the certainty of evidence was very low, the GDG placed a high value on the potential for improved outcomes with transfusion therapy in this high-risk population. The recommendation assumes that hydroxyurea is already part of comprehensive care for all children aged 9 months and older with SCD. In this context, regular blood transfusion and chelation are considered additional interventions specifically targeting secondary stroke prevention.

The GDG acknowledged that in settings where regular transfusion may not be feasible or is declined, hydroxyurea remains preferable to no treatment at all. Although the harms and burdens of chronic transfusion and iron chelation, such as iron overload and alloimmunization, are recognized, they are not considered prohibitive when weighed up against the substantial risk of recurrent stroke. The conditional nature of the recommendation reflects the limited evidence and the need for individualized, context-sensitive implementation.

Summary of evidence

The systematic review identified one RCT and one NRS *(98, 206)*. The SWiTCH trial randomized 134 children and compared treatment with hydroxyurea to no hydroxyurea. This trial also assessed the role of hydroxyurea therapy compared to regular RBC transfusion alone in preventing secondary strokes *(98)*. In this RCT, there were seven out of 66 stroke episodes in the hydroxyurea arm after 30 months of follow-up as opposed to none in the blood transfusion group (RR: 14.78; 95% CI: 0.86–253.59). Mortality occurred in one out of 67 (1.5%) and one out of 66 (1.5%) in both arms. Furthermore, the trial reported that switching from long-term transfusions to hydroxyurea may increase some SCD-related serious adverse events, such as painful crises (RR: 3.15; 95% CI: 1.23–8.11) *(98)*.

The NRS had two phases: phase 1 included 16 patients who underwent abrupt discontinuation of transfusion and started hydroxyurea therapy. Phase 2 included 35 children with SCA who were divided into two arms: 15 patients underwent abrupt discontinuation of transfusion to start hydroxyurea therapy while 20 patients had overlapping hydroxyurea and blood transfusion *(206)*. There were five out of 15 (33%) episodes of stroke in the hydroxyurea group compared to two out of 10 (10%) in the blood transfusion arm. In addition, children on hydroxyurea (n = 15) received serial phlebotomy and had lower mean serum ferritin values than children on transfusions (n = 20) (591 ng/mL vs 3410 ng/mL) after 5.6 years of therapy. All the critical outcomes of interest reported in the SWiTCH trial were determined as low certainty of evidence and in the NRS they were determined as very low certainty of evidence. No evidence was identified regarding quality of life, school absenteeism, use of analgesics and health service utilization.

Benefits and desirable effects

Evidence from the SWiTCH trial and the NRS suggests that hydroxyurea therapy alone, even at the maximum-tolerated dose, is less effective than regular blood transfusion for secondary stroke prevention in children and adolescents with SCD. In the SWiTCH trial, the incidence of secondary stroke was significantly higher in the hydroxyurea arm (4.2 events per 100 patient-years compared with zero events per 100 patient-years), indicating the superiority of regular transfusion therapy. The NRS further supported these findings, with an estimated 233 additional secondary strokes per 1000 patients treated with hydroxyurea alone compared to blood transfusion. However, the period of overlap therapy, during which hydroxyurea was escalated to the maximum-tolerated dose before discontinuing transfusions, was associated with a greater reduction in secondary stroke risk. Among children receiving overlap therapy, four of 20 (20%) patients experienced stroke (median: 2.6 years), while six of 15 (40%) patients without overlap therapy had recurrent stroke (median: 0.94 years) (P = 0.006). Overall, these findings indicate that, although hydroxyurea therapy provides a small benefit in reducing secondary stroke risk, regular blood transfusion remains the effective strategy. However, both hydroxyurea alone and regular blood transfusion therapies are superior to no intervention.

Harms and undesirable effects

The potential harms associated with regular blood transfusion therapy have been outlined in several studies for primary and secondary prevention of stroke in children with SCD. The SWiTCH trial reported significantly higher total SCD-related serious adverse events with hydroxyurea therapy compared to blood transfusion (RR: 3.10; 95% CI: 1.42–6.75) but infections and infestations were comparable *(98)*. In the NRS, children on hydroxyurea and serial phlebotomy had lower mean serum ferritin values than children on transfusions (591 ng/mL vs 3410 ng/mL; *P* = 0.02) after 5.6 years of therapy *(206)*. Nonadherence, due to sensitivity from the blood transfusions, was also observed. Other known adverse events for regular blood transfusion include excessive iron stores that requires chelation therapy, alloimmunization and adverse blood transfusion reactions *(97, 207-209)*. Known hydroxyurea therapy adverse effects include dose-related haemopoietic suppression leading to neutropenia, thrombocytopenia and reticulocytopenia *(77, 81, 83, 84)*.

Other considerations

Preferences, values and acceptability: The GDG identified potential variability and uncertainty in how patients and caregivers value the prevention of recurrent stroke in children and adolescents with SCD. Blood transfusion was generally viewed as more acceptable, particularly when caregivers understood its life-saving potential in severe cases. However, concerns about iron overload, alloimmunization and the burden of chronic transfusion may lead some families to decline this option. Hydroxyurea therapy, although widely used as standard care, may be met with hesitation due to perceived risks and side-effects. This reluctance may be more pronounced among those who perceive their child's SCD as mild or stable *(99)*. Caregivers of children with more severe SCD manifestations are more likely to accept either or both regular blood transfusion and hydroxyurea therapy as part of a comprehensive preventive strategy.

The GDG emphasized the importance of shared decision-making, taking into account individual risk profiles, caregiver concerns and the availability of resources. Tailored communication and education are essential to support informed choices and improve the acceptability of recommended interventions.

Resources required: These are highly variable depending on the hospital setting or blood bank where regular blood transfusions are provided. Typical resources required are a haematologist, transfusion medicine expert and an extensive blood bank for minor RBC matching. Regular blood transfusion also requires skilled paediatric nurses for monthly IV access or a paediatric surgeon for central catheter placement. Resources required for hydroxyurea therapy include knowledge of how to administer the medication and the skills required to monitor for the toxicities associated with hydroxyurea. Compared to blood transfusion, hydroxyurea intervention is more cost-effective. Hydroxyurea is less costly than regular blood transfusion and eventual iron chelation therapy but it is less effective for secondary stroke prevention.

Equity: Although chronic transfusion therapy is widely used across different populations and has been used as a treatment for various SCD-related morbidities with regular monitoring for iron overload and transfusion-related adverse events, there have been concerns about therapy cost, safety of blood transfusion and limited blood supply in various settings. It will probably increase equity, but its acceptability might vary.

Feasibility: The GDG determined that it is probably feasible in most settings. However, the GDG noted that regular blood transfusion is resource-intensive, and require frequent hospital visits and commitment from the family and caregivers. Family preferences and the inconvenience and financial resources associated with regular blood transfusion therapy may impact on compliance.

Implementation considerations

- Caring for children in situations in which caregivers have strong beliefs against blood transfusion therapy may require additional counselling and, in some cases, a court order might need to be obtained in the best interest of the child to provide the maximum benefit of decreasing future stroke recurrences.

Research gaps

Further research is needed to strengthen the evidence base for secondary stroke prevention in children and adolescents with SCD, particularly in relation to the comparative effectiveness, feasibility and contextual appropriateness of available interventions. The following areas were identified as priorities for future research.

- Multicentre RCTs comparing regular blood transfusion with hydroxyurea monotherapy, including dosing strategies, for the prevention of secondary stroke.
- Cost-effectiveness analyses studies evaluating the trade-offs between preventing additional strokes and the costs associated with universal hydroxyurea use versus chronic transfusion and iron chelation therapy.
- High-quality implementation research to generate evidence on contextual factors such as acceptability, feasibility, resource use, cost-effectiveness, equity, and patient and caregiver values.
- Studies on novel therapeutic strategies for secondary stroke prevention, particularly in low-resource settings where access to chronic transfusion and chelation therapy is limited.

3.7 Screening for complications in children with SCD

3.7.1 Routine screening with PFT

Background

Abnormal lung function or chronic lung disease, diagnosed by pulmonary function testing (PFT), is relatively common among children and adolescents with SCD *(210)*. Children and adolescents with SCD may show abnormal restrictive physiology but have more predominantly obstructive disease *(211, 212)*. One retrospective study in children and adolescents with SCD demonstrated abnormal PFT results of obstructive physiology in 35% and restrictive physiology in 26% *(211)*. Increasing age, a family or patient history of asthma or wheezing, and increased haemolysis have been associated with obstructive physiology. However, several aspects of abnormal lung function remain unclear, including its prevalence, natural history, relationship to disease severity and optimal therapy.

Although knowledge and recognition of the pulmonary complications of SCD have improved over the last few decades, there remains no specific treatment for these conditions. Currently, it is not clear whether conventional treatment regimens directed at non-SCD populations have equivalent efficacy in patients with SCD. Despite the utility of PFT as a diagnostic tool for individuals with signs and symptoms suggestive of chronic respiratory impairment, its effectiveness as a screening tool for asymptomatic individuals with SCD is not clear. The impact of results from screening on changing management and patient-important outcomes is also unknown.

No recommendation:

WHO makes no recommendation on the routine use of PFT in children and adolescents (aged 0–19 years) with SCD.

Remarks

- The GDG decided not to make a recommendation due to insufficient and indirect evidence. Available studies on PFTs in children and adolescents with SCD were not designed to address the specific PICO question and did not demonstrate clear clinical benefit.
- There is currently no established link between abnormal PFT findings and actionable changes in clinical management that would improve outcomes or quality of life in this population.
- Performing PFTs in children aged less than 5 years is particularly challenging due to limited cooperation and test feasibility.
- Routine screening may carry unintended consequences, such as increased anxiety, unnecessary follow-up investigations or treatments without proven benefits.
- Although abnormal PFTs may help monitor pulmonary function over time, their role in routine screening for asymptomatic children with SCD remains unclear.

Summary of evidence

No relevant studies were identified to answer this specific question. The GDG withheld any decision on this PICO question until further evidence is obtained.

3.7.2 Routine screening with echocardiography

Background

Cardiac complications of SCD are due to chronic anaemia, VOC, iron overload, pulmonary, renal and hepatic damage and are a major cause of morbidity and mortality *(213-215)*. Cardiac complications in children with SCD are mainly dilated or restrictive cardiomyopathy and pulmonary hypertension, although sudden death and acute cardiac failure due to myocardial infarction or arrhythmias may also occur *(216-220)*. Pulmonary hypertension is defined as a mean pulmonary artery pressure of ≥25 mmHg at rest or ≥30 mmHg during exercise, as determined by cardiac catheterization, irrespective of age except in infancy *(221)*. Studies in children report a prevalence of approximately 30% of children with SCD having elevated pulmonary artery pressures measured by echocardiography *(216, 218, 219)*. Pulmonary hypertension ultimately leads to straining of the right ventricle and increases the risk of heart failure in affected patients *(213)*. The clinical presentation of pulmonary hypertension in the early stages is usually nonspecific, and early symptoms are similar to those of many other diseases that present with dyspnoea on exertion, thus, delaying the diagnosis and management *(222-224)*.

Pulmonary hypertension may result in decreases in quality of life and life expectancy, suggesting that it is a priority to detect pulmonary hypertension early and provide applicable interventions to slow down or prevent the disease course *(225, 226)*. The gold standard measurement for mean pulmonary artery pressure is right-sided heart catheterization, but this method is highly invasive and not suitable for screening purposes *(219)*. Measurement of tricuspid regurgitant velocity (TRV) by Doppler echocardiography to estimate pulmonary artery systolic pressure has been found to be the most accurate non-invasive method to determine pulmonary hypertension *(219, 227)*. However, data are limited in children, and it is unclear whether TRV is associated with pulmonary hypertension in the same way that it is in adults, and its clinical significance in paediatric patients is also unclear *(224, 227-232)*.

In many cases in children, a high TRV may represent haemodynamic changes due to high cardiac output and the risk of death is low overall; hence, the suggested cut-off value is ≥2.7 m/s rather than 2.5 m/s, which is used in adults *(221, 227)*. For these reasons, the recommendations for screening have not yet been established. Some guidelines advocate that screening be reserved for children presenting with additional risk factors that suggest the development of early vasculopathy, such as dyspnoea, hypoxaemia, symptoms of right heart failure, or laboratory measures of high levels of haemolysis or urine proteinuria, which are associated with haemolysis and increased risk of vasculopathy *(120)*. In addition, despite the utility of Doppler echocardiography as a diagnostic aid for pulmonary hypertension, its effectiveness as a screening tool for pulmonary hypertension in asymptomatic children and adolescents with SCD, and the impact on clinical outcomes is not clear.

Recommendation 13:

In children and adolescents (aged 0–19 years) with SCD who have no symptoms of pulmonary hypertension, routine echocardiogram screening to detect pulmonary hypertension is not suggested.

Conditional recommendation, low certainty of evidence.

Remarks

- Echocardiography may be appropriate in the presence of clinical signs or symptoms suggestive of pulmonary hypertension, such as persistent respiratory distress, recurrent hypoxaemia, chest pain at rest or with exertion, or other indicators of cardiopulmonary compromise.
- This recommendation reflects the limited evidence supporting the clinical utility of routine echocardiographic screening in asymptomatic individuals and the potential for unnecessary follow-up testing or interventions without proven benefit.

Justification

The GDG made a conditional recommendation against routine echocardiographic screening for pulmonary hypertension in asymptomatic children and adolescents with SCD. This decision was based on the absence of direct comparative evidence demonstrating benefit in patient-important outcomes, and the overall low certainty of evidence supporting routine screening. Although echocardiography is a non-invasive and widely available tool that can estimate TRV, a potential marker of pulmonary hypertension, there is limited evidence linking elevated TRV values to long-term clinical outcomes in children with SCD.

Moreover, there is insufficient evidence to determine whether changes in clinical management based on screening echocardiogram findings lead to improved health outcomes. In the absence of a clearly actionable intervention following detection and, given the uncertainty around the prognostic value of TRV in this population, the GDG concluded that routine screening in asymptomatic individuals is not justified. However, echocardiography may still be warranted in symptomatic patients based on clinical judgement.

Summary of evidence

The systematic review identified eight studies, four retrospective, three prospective and one cross-sectional, which were mostly conducted in high-income countries (n = 6) *(229, 233-239)*. A total of 1337 participants with SCD were recruited, and all eight studies included children and adolescents aged 1–19 years, although four also included adult participants. Seven studies classified the presence of pulmonary hypertension by a TRV ≥2.5 m/s, while one study specified a TRV ≥2.55 m/s, but the frequency of screening was not well defined, except for annual screening in one study. No studies confirmed the presence of pulmonary hypertension using the gold standard of cardiac catheterization or implemented a comparator. A meta-analysis was not feasible for the identified data due to the heterogeneity of reported outcomes and study features.

Two retrospective studies reported on echocardiography screening, clinical management and outcomes *(229, 237)*. In a retrospective chart review with a mean follow-up of 43 months, 22% of patients with TRV values above 2.5 m/s (n = 120) initiated hydroxyurea treatment compared to 6% of patients with TRV values below 2.5 m/s (n = 120). Patients newly initiated on hydroxyurea (n = 26) had a greater reduction in TRV compared to those not initiated on hydroxyurea (n = 53) (TRV reduction: –0.32 (±0.25) vs –0.25 (±0.41)) *(229)*. There was no difference in the TRV values of patients who initiated transfusion. In another study of 90 patients with a follow-up of 4 years, five out of 29 patients (17%), who had normal TRV (<2.5 m/s) at initial inspection and were on hydroxyurea, developed abnormal TRV (≥2.5 m/s) during follow-up *(237)*. The authors concluded that hydroxyurea did not prevent the development of pulmonary hypertension *(229, 237)*.

Only two deaths in 194 patients were reported in the three studies that assessed mortality: one death had a normal TRV of <2.5 m/s *(239)*, the other death had an abnormal TRV of ≥3.0 m/s *(233)*, and one study did not report any death *(236)*. Hence, the reviewers concluded that echocardiography findings were not related to mortality. No direct comparisons were available for all other relevant clinical outcomes.

Benefits and desirable effects

The GDG recognized that there were no direct head-to-head comparisons of the benefits in children and adolescents with SCD who underwent screening echocardiography to identify pulmonary hypertension versus those who did not. In addition, the GDG noted the limitations associated with using echocardiography TRV values as a marker of long-term severity. High TRV values may not be synonymous with pulmonary hypertension and were not associated with mortality. There were no clear benefits of performing echocardiography, as demonstrated by the studies, and it was not clear if abnormal TRVs are useful. The GDG determined that they did not know if there were any benefits, and therefore routine echocardiography screening could not be a standard of care. However, it could be used as a prognostic biomarker for pulmonary hypertension in determining a baseline condition, particularly as adolescents transition to adulthood. However, echocardiography may be of possible benefit in examining cardiac performance

in children with symptomatic SCD. The GDG decided that there was very low certainty of evidence for any health benefit related to the patient-important outcomes associated with routine echocardiography screening in asymptomatic children with SCD.

Harms and undesirable effects

No adverse events were reported related to echocardiography screening. There are likely to be few negative effects from routine echocardiography because it is non-invasive, so the GDG judged it as trivial. However, possible downstream harms could include the unnecessary use of the information obtained from screening, anxiety for patients and increased health care costs from unnecessary testing without changes in clinical management. In addition, the psychological effects of a test on the heart may be considered serious by parents.

Other considerations

Preferences, values and acceptability: The GDG decided that patients and their parents may value the main outcome being measured even though the test is not measuring pulmonary hypertension. However, parents who are well informed about the test might not be as favourable, although some might want as much information as possible. It may not be acceptable to clinicians because of the uncertainty of the value of the test in measuring pulmonary hypertension.

Resources required: There were no studies included that looked at the resources required. However, the GDG determined that the direct cost of conducting routine echocardiography screenings in LMICs is moderately large, primarily due to the equipment required and the training of personnel. If used routinely, the GDG judged that it cannot be cost-effective.

Feasibility: The feasibility of echocardiography screening may vary based on the availability of financial resources as well as the technical aspects and skills required for accurate measurement of TRV. Implementation considerations for echocardiograms in these situations should address the cost of the equipment, especially the probes, and the trained personnel required. In health systems that are overburdened, more staff may be needed, adding cost and strain to the system.

Research gaps

Further research is needed to clarify the role of echocardiography screening in the management of children and adolescents with SCD. Specifically, the following areas warrant investigation.

- Evaluation of the impact of echocardiography screening on quality of life and clinical outcomes in children and adolescents with SCD, including the identification of clinical scenarios in which screening may be most beneficial. This evidence could support more patient-centred care and inform treatment decision-making.
- Assessment of the feasibility, utility and cost-effectiveness of echocardiography screening in LMICs, where access to diagnostic imaging and follow-up care may be limited.

3.7.3 TCD screening to prevent stroke

Background

SCD is the most common cause of childhood stroke, which occurs in up to 11% of children with SCA with a peak between the ages of 2 and 9 years *(187, 191)*. The incidence of a subsequent stroke is 50–90% within 3 years of the first event *(201)*. The medium-sized arteries of the circle of Willis, including the carotid arteries, are particularly vulnerable to the effects of sickled RBCs and chronic haemolysis *(240)*. Patients are at risk of both ischaemic and haemorrhagic strokes, with ischaemic strokes occurring mostly in childhood *(191)*. In children who have had a stroke, chronic transfusions have been shown to reduce the risk of recurrent stroke *(98, 191, 201, 206)*.

TCD has been shown to accurately predict those children aged 2–16 years who are at risk of stroke so that appropriate preventive treatment can be commenced *(241, 242)*. TCD by ultrasound measures blood flow velocities through the brain's blood vessels (either the internal carotid artery or the middle cerebral artery). TCD velocities are classified as normal if they are <170 cm/second; conditional if they are 170–199 cm/s; or abnormal if they are ≥200 cm/s *(191)*. A mean velocity of ≥200 cm/s is associated with a 46% risk of cerebral infarction over 39 months *(191)*. The Stroke Prevention Trial in Sickle-Cell Anaemia (STOP) demonstrated that regular TCD screening combined with transfusions reduces the risk of first stroke by 92% in children with abnormal TCD *(191)*. As a result, TCD screening has become the clinical standard of care for children with SCA in many settings, particularly in high-income countries where it has significantly reduced the risk of stroke in children with SCA *(243)*. In addition to its role in stroke prevention, TCD screening holds promise in predicting cognitive impairment in children with SCA *(244, 245)*. By detecting abnormalities in blood flow velocities, TCD screening provides valuable insights into the risk of primary stroke and cognitive decline in children with SCA.

Recommendation 14:

In children and adolescents (aged 2–16 years) with SCA and no prior abnormal TCD results, annual TCD ultrasound screening is recommended for primary prevention of stroke.

Strong recommendation, very low certainty of evidence.

Remarks

- Early identification of children at increased risk of stroke through TCD screening enables timely intervention and may help prevent serious complications such as stroke.
- In low-resource settings, standard ultrasound machines may be adapted for TCD screening using the appropriate probes, along with training of health care personnel at lower-level facilities.
- Patients and their families should be informed about the importance of stroke risk assessment and available options for primary stroke prevention, including regular TCD screening and follow-up care.

Justification

The GDG made a strong recommendation for annual TCD screening in children and adolescents with SCA aged 2–16 years who have no prior abnormal TCD results, despite the very low certainty of evidence. This decision was based on the critical importance of early identification and management of children at high risk of stroke to prevent long-term neurological damage. Evidence from RCTs and NRSs demonstrates a large benefit in identifying and treating children with abnormal TCD velocities (>200 cm/s), which are associated with significantly increased stroke risk.

The GDG judged that the harms of not screening, particularly the risk of missing children with conditional or abnormal TCD values, outweigh the uncertainty in the evidence. Without intervention, approximately 11% of untreated children with abnormal TCD results may experience symptomatic stroke. TCD screening is non-invasive, feasible to implement in most settings, and can be adapted for use in first-level facilities in LMICs where ultrasound machines are available. Furthermore, treatment options such as hydroxyurea and blood transfusion are increasingly accessible in these settings. Although resource requirements may be moderate, the GDG concluded that the intervention is acceptable, feasible and justified by the potential to prevent severe and irreversible complications.

Summary of evidence

The systematic review identified a meta-analysis that included one RCT and eight NRSs that assessed the role of TCD screening and transfusion therapy in children with SCA and no previous stroke risk *(246)*. Four studies assessed stroke incidence and risk based on TCD results and found a significant association between stroke risk and TCD result *(246)*. Seven studies assessed the impact of implementing TCD screening programmes and found that they had a positive impact on stroke prevention *(246)*. The STOP trial was designed to assess whether chronic transfusion could prevent initial stroke in children with SCA who are at high risk of stroke, as determined by TCD *(191)*. It was conducted across 14 different trial sites from 1995 to 1997 and was terminated early in 1997 due to the significantly increased risk of stroke among patients receiving standard care compared to patients who received transfusion therapy. The NRSs included retrospective (n = 6) and prospective (n = 5) studies conducted mainly in high-income countries that used convenience sampling (n = 10), and outcomes assessed include stroke (n = 8) and neurocognitive function (n = 3). Studies primarily used the 2-MHz pulsed Doppler ultrasonography system and the STOP velocity thresholds i.e. normal: <170 cm/s in all arteries; conditional: 170–200 cm/s; and abnormal: ≥200 cm/s in the internal carotid artery or middle cerebral artery.

The STOP trial transfusion was implemented in the intervention arm to achieve HbS concentrations below 30% of total haemoglobin level. A combination of simple (63%), exchange (12%) and combination transfusions (25%) were used. The RCT demonstrated that chronic transfusion therapy for children with abnormal TCD results reduced the risk of stroke by 92% ($P < 0.001$) compared to standard care. During the mean follow-up period of 19.6 months, stroke occurred in 1.6% (one out of 63) of transfused patients versus 16.4% (11 out of 67) in the standard of care group (RR: 0.10; 95%CI: 0.01–0.73), or 148 fewer per 1000 patients (from 163 fewer to 44 fewer). The trial was stopped early due to clear benefit, but certainty of evidence was very low due to unblinding and early termination.

Seven studies evaluating TCD implementation reported a substantial reduction in stroke incidence after screening programmes were introduced *(246)*. A pooled analysis of three NRSs that compared stroke incidence before and after TCD implementation showed a significant decrease in stroke incidence in the post-TCD period *(246)*. The pooled rate ratio of stroke was 0.19 (95% CI: 0.07–0.46), equivalent to approximately four fewer strokes per 1000 patient-years (95% CI: 5–3). Certainty of evidence was rated low due to the observational design and potential confounding.

In the three studies that examined cognitive impairment, TCD velocities were associated with greater impairment in frontal neurocognitive functions, including verbal intelligence, executive function and working memory *(244, 245, 247)*. For example, children with abnormal TCD values (>200 cm/s) scored lower on verbal IQ and executive function (using the Wechsler Abbreviated Scale of Intelligence) compared to those with conditional velocities (<170 cm/s) *(247)*). Certainty of evidence was very low due to small sample sizes and observational design.

Overall, abnormal TCD results were significantly associated with increased stroke incidence and are reliable predictors of stroke risk in children with SCA. Implementing screening and initiating transfusion therapy for high-risk patients significantly reduce stroke incidence. However, certainty of evidence for neurocognitive outcomes and long-term programme impact remains low to very low. TCD screening should be considered a reliable tool for primary stroke prevention in SCA as it identifies children with SCD at higher risk of stroke and, when combined with transfusion, may lower stroke incidence.

Benefits or desirable effects

The GDG determined that annual TCD screening offers substantial benefits for the primary prevention of stroke in children and adolescents with SCA. TCD screening enables early identification of individuals with elevated stroke risk, particularly those with abnormal TCD velocities (>200 cm/s), allowing timely initiation of preventive interventions such as regular blood transfusion *(246)*.

Evidence from the RCT (STOP trial) demonstrated a significant reduction in the incidence of first stroke among children with abnormal TCD measurements who received regular blood transfusion therapy compared to those who were only observed *(191)*. Additional evidence from NRSs showed a marked decrease in stroke incidence following implementation of TCD screening programmes compared to pre-implementation periods *(248-250)*. Moreover, abnormal TCD velocities have been associated with greater impairment in frontal lobe neurocognitive functioning, suggesting that early detection and intervention may also help preserve cognitive outcomes *(246)*.

Given the high burden of stroke in children with SCA and the potential for TCD screening to enable effective primary prevention, the GDG concluded that the desirable effects of this intervention are large. The group emphasized the importance of offering families the opportunity to assess stroke risk and access preventive care.

Harms and undesirable effects

The GDG noted that TCD is a non-invasive and relatively safe intervention, with possible discomfort from mild skin irritation from the gel or dizziness, and judged the undesirable effects as trivial. However, the GDG recognized the downstream consequences of potential known adverse events associated with regular blood transfusion and hydroxyurea therapy for those children identified with abnormal TCD velocities *(81, 83, 143)*. Downstream negative effects to consider include an increase in serum ferritin and increased risk of alloimmunization due to treatment, and the fact that patients with abnormal values are screened more regularly than patients with normal values.

Other considerations

Preferences, values and acceptability: Stroke and intellectual impairment are major issues in SCA. Children and caregivers are likely to prioritize TCD screening and stroke prevention therapy. The GDG considered cost, lack of expertise, insufficient blood banks, cultural and religious factors, as well as proximity to health facilities. The GDG decided there was no important uncertainty or variability in how much patients and their families would value the outcome, although the GDG noted that in LMICs specific considerations are required to address scepticism and safety concerns regarding blood transfusion and hydroxyurea therapy. The GDG determined that TCD screening, being a non-invasive procedure, is more likely to be acceptable to children with SCA, their caregivers and their clinical care providers, including other stakeholders, because the intervention can lead to the prevention of stroke.

Resources required: None of the included studies assessed cost-effectiveness. The GDG noted that despite the lack of a systematic assessment of the cost-effectiveness studies, preventing stroke in children is more likely to be less expensive than the long-term consequences of stroke complications and disabilities. However, the GDG determined that the resources required will vary depending on the health system and setting, but agreed on moderate costs for TCD screening plus stroke preventive therapy. In one cost-effective analysis study conducted in a high-income country, TCD screening and transfusion for patients at high risk of stroke was found to be cost-effective with an incremental cost-effectiveness ratio of £24 075 per quality-adjusted life-year gained and helped to avoid 68 strokes over the lifetime of a population of 1000 patients *(251)*. In one study from a high-income country, the cost of TCD screening was estimated to be US$ 371 per test; however, in Uganda, a low-income country, the direct cost for TCD screening was estimated to be US$ 50 *(248)*. In settings where ultrasound machines are not readily available, the cost of purchasing the equipment and probes is likely to be moderate compared with the cost of ultrasound machines.

Equity: The recommendation could be a burden on families and hospitals, and thereby impact equity. The GDG acknowledged that, in settings where ultrasound machines are not readily available, this could lead to referrals to specialty centres which could lead to equity concerns. If the test is freely or easily available, then it would increase equity. Some people may be disadvantaged because TCD requires moderately large resources.

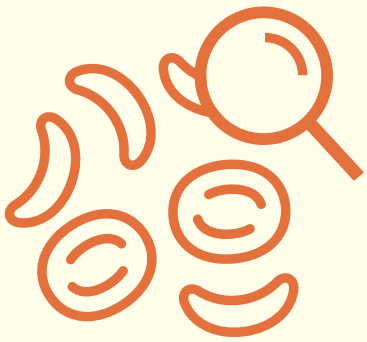
Feasibility: The GDG acknowledged some caveats regarding feasibility but reiterated that, despite possible anticipated challenges in some LMICs, it would be more cost-effective and equitable for health care systems to prevent strokes in children with SCA. The ability to scale up competency to carry out TCD was discussed by the GDG, and there was general agreement that nurses and radiographers would be able to perform the test without the need for extensive training. Therefore, where first-level referral facilities already have ultrasound machines available they will only need TCD probes, meaning that not only tertiary referral centres would be able to conduct the test. However, it will also require the training of personnel at lower-level facilities to provide hydroxyurea and exchange transfusion therapy. Before capacity-building is scaled up for the provision of both treatment options, patients may need to be sent to tertiary referral centres for exchange transfusion. The GDG determined that the feasibility of implementing TCD screening was variable; however, the cost of equipment would be challenging unless it is covered by national programmes.

Research gaps

Further research is needed to strengthen the evidence base for the use of TCD screening in the primary prevention of stroke among children and adolescents with SCA. The following areas have been identified as priorities for future research.

- Since all studies included in the review had a high risk of bias, well-designed clinical trials and robust observational studies are needed to confirm current findings and support clinical management.
- Most studies focused exclusively on children with SCA (HbSS). Research should assess the impact of TCD screening on other SCD genotypes (e.g. HbSC, HbSβ^+-thalassemia) to determine whether findings can be generalized to these sub-populations.
- Studies are needed to assess how routine TCD screening influences health-related quality of life, psychological well-being and caregiver burden.
- Studies are needed to evaluate the operational feasibility, training requirements and health system adaptations needed to implement TCD screening in primary or district-level facilities, particularly in LMICs.
- Studies are needed to explore and evaluate alternative interventions to regular blood transfusion for children identified as high risk through TCD screening, including the role of hydroxyurea or emerging therapies.
- Longitudinal studies are needed to assess the impact of early intervention (e.g. transfusion or hydroxyurea) initiated based on elevated TCD velocities on cognitive development and academic performance.
- Comparative studies are needed to evaluate the diagnostic accuracy, feasibility and clinical utility of 4TCD imaging as an alternative to standard TCD for stroke risk screening in children with SCA.

4. Monitoring and evaluation



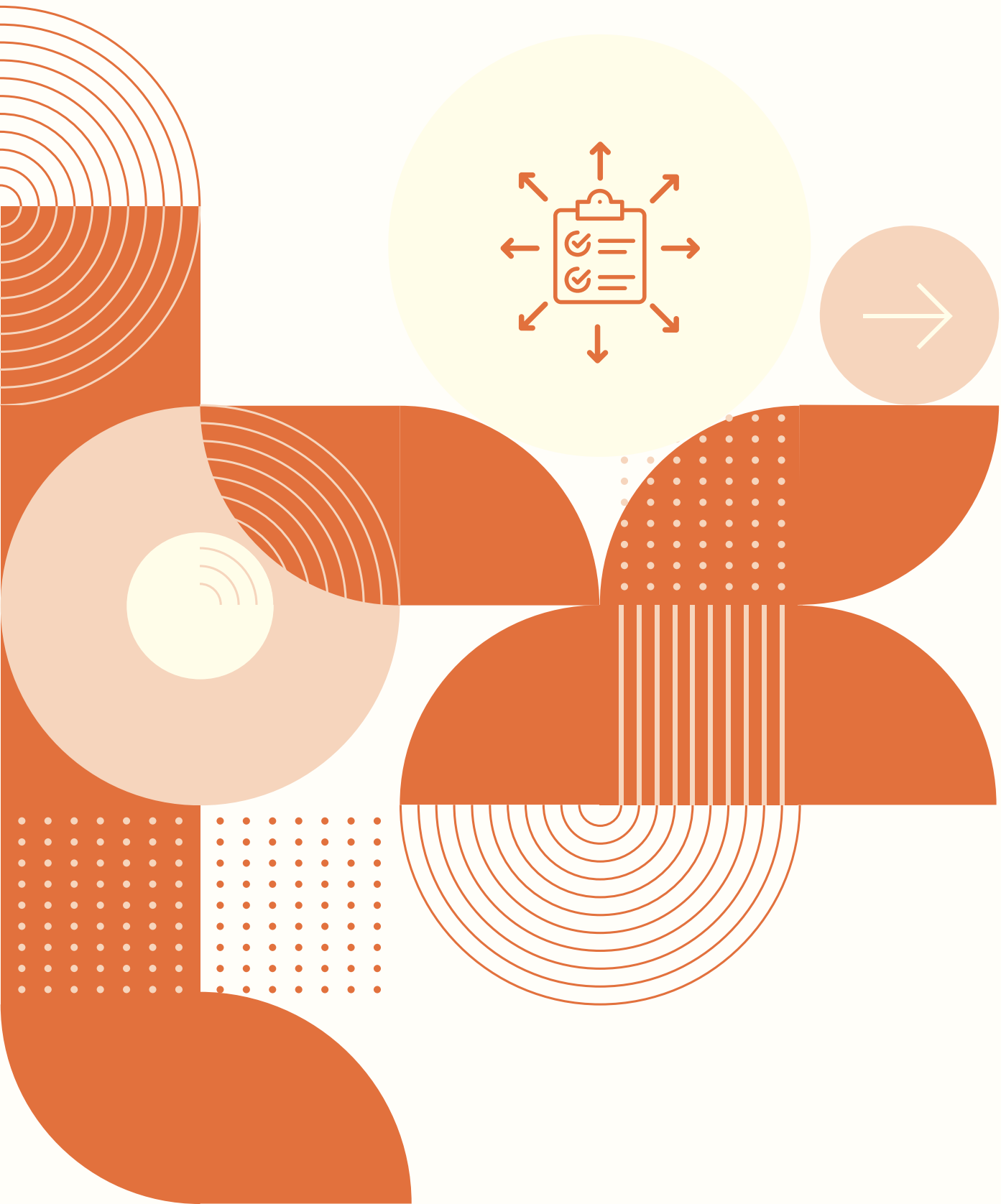
Monitoring and evaluation will be built into the dissemination and implementation process to provide data and information on uptake, implementation and impact of this guideline. In collaboration with the monitoring and evaluation team of the Department of Sexual, Reproductive, Maternal, Child and Adolescent Health and Ageing, WHO, the data on country- and regional-level adoption of the recommendations will be monitored and evaluated in the short-to-medium term in Member States, Key components of the monitoring and evaluation include:

- short-to-medium term country-level adoption and integration of the recommendations into national policies, clinical guidelines and training curricula;
- use of the WHO sexual, reproductive, maternal, newborn, child and adolescent health policy survey *(252)*, which is conducted every 4 years, to collect standardized data on policy alignment, implementation status and the coverage of the recommended interventions;
- monitoring of derivative product uptake, including updates to the *Pocket book of hospital care for children (18)*, the *Integrated management of childhood illness (IMCI) chart booklet (19)* and associated training tools; and
- assessment of implementation fidelity through country reports, programme reviews and stakeholder feedback.

Where feasible, WHO will support countries in strengthening their national health information systems to include indicators relevant to SCD management, such as access to hydroxyurea, availability of blood transfusion services and coverage of secondary stroke prevention interventions.

Findings from monitoring activities will inform future updates of the guideline and guide technical assistance to Member States. WHO will also explore opportunities to align with broader NCD and child health monitoring frameworks to ensure coherence and efficiency in data collection and use.

5. Dissemination, adaptation and updating



5.1 Dissemination strategy

This is global guideline and these recommendations are intended to inform national and subnational policies and clinical practices. Member States are encouraged to adapt the recommendations to their specific context, considering feasibility, resource availability, health system capacity and epidemiological profile. WHO will disseminate the guideline through multiple channels to ensure broad reach and uptake by:

- publication on the WHO website, and inclusion in the WHO Digital Health Repository (https://iris.who.int);
- targeted webinars and virtual briefings for WHO regional and country offices, ministries of health, professional associations, WHO collaborating centres, academic institutions, United Nations agencies and nongovernmental organizations;
- incorporation into key WHO-endorsed derivative clinical tools to support implementation at the point of care; and
- the development of a digital adaptation kit to support country-level digitization and integration into electronic clinical decision-support tools.

5.2 Derivative products for the recommendations

These SCD recommendations are part of the consolidated evidence for updating the *Pocket book of hospital care for children (18)* and the *Integrated management of childhood illness (IMCI) chart booklet (19)*. They will also be incorporated into other key WHO-endorsed clinical tools to support implementation at the point of care:

- at the primary care level, using the IMCI clinical guidelines algorithms *(19)*;
- in first-referral hospitals, using the *Pocket book of hospital care for children (18)*; and
- in IMCI generic training manuals, orientation courses, assessment tools and job aids.

5.3 Adaptation by Member States

Member States are expected to adapt the recommendations to their own contexts using a structured approach supported by WHO regional and country offices. Although intensive adaptation process may not be required in most settings, ministries of health should:

- update national standard treatment guidelines in alignment with the *Pocket book of hospital care for children (18)* and the IMCI clinical guidelines algorithms *(19)*;
- revise training curricula for health care workers to reflect the updated clinical algorithms;
- review and update the national paediatric essential medicines list and the diagnostic supplies list; and
- develop a capacity-building plan to ensure health workers are equipped to implement the recommendations effectively.
- The recommendations have been designed to align with commonly used clinical decision-making algorithms, facilitating easier integration into existing child health programmes and service delivery models.

5.4 Updating the guideline

This guideline will be maintained as a living document, meaning that new and emerging evidence relevant to the prevention, diagnosis and management of SCD in children and adolescents will be continuously monitored and assessed. Where new evidence has the potential to change current recommendations, WHO will initiate a targeted update to ensure the guidance remains current, relevant and evidence-based.

The WHO Secretariat, led by the Department of Sexual, Reproductive, Maternal, Child and Adolescent Health and Ageing, will coordinate in collaboration with internal WHO departments and experts. Priority will be given to areas where the certainty of evidence is low or very low, and where new interventions, technologies or implementation strategies emerge.

In addition to ongoing updates, a formal review of the guideline will be conducted 5 years after publication, unless compelling evidence warrants an earlier revision. This review will include:

- systematic reviews of the relevant new evidence;
- appraisal of the need for updating or revalidating the existing recommendations; and
- stakeholder consultations to define the scope of any revisions.

This approach ensures that the guideline remains a dynamic and responsive tool for improving care and outcomes for children and adolescents with SCD globally.

6. Implementation of the recommendations

This section provides practical guidance for translating the guideline's 15 recommendations into action across diverse health system contexts. Recognizing the variability in resources, infrastructure and capacity among countries, the guidance emphasizes the need for clarity and consistency for all end-users. Effective implementation is essential to ensure that these evidence-based recommendations lead to improved health outcomes for children and adolescents living with SCD.

The guideline comprises 15 recommendations: 13 are conditional and require contextual adaptation and phased implementation due to low or very low certainty of evidence; two are strong recommendations prioritized for immediate action despite low certainty; and two areas have no recommendation, highlighting the need for further research and reliance on clinical judgement.

To achieve meaningful impact, implementation strategies should focus on flexibility, capacity-building and clear communication. Countries are encouraged to adapt, prioritize and integrate these interventions into existing health programmes in a sustainable and equitable manner. Embedding stakeholder engagement and accountability mechanisms within national implementation plans will enhance the adoption and acceptance of the recommendations.

6.1 General principles for implementation

1. **Contextual adaptation:** Countries should adapt recommendations to local epidemiology, health system capacity and resource availability. Conditional recommendations require prioritization based on feasibility, equity and cost-effectiveness.
2. **Integration into national NCD strategies:** These recommendations should be incorporated into national NCD strategies, including PEN-Plus implementation plans, to strengthen service delivery for children and adolescents with SCD.
3. **Integration into existing platforms:** Recommendations should be embedded within child health programmes, essential medicines lists and national treatment protocols. Where possible, leverage maternal and child health services for screening, prophylaxis and chronic care.
4. **Capacity-building and training:** Health workers need training on diagnostic tools (including POCTs), hydroxyurea administration, pain management protocols and transfusion safety. Job aids and decision-support tools should be developed to guide conditional recommendations.
5. **Supply chain and resource planning:** Ensure the availability of hydroxyurea, penicillin, diagnostic POCTs and transfusion services. Plan for iron chelation therapy where chronic transfusion is recommended.
6. **Shared decision-making:** Engage caregivers and patients in understanding benefits, risks and uncertainties, especially for conditional recommendations. Provide culturally appropriate information to support informed choices.

6.2 Addressing conditional recommendations

Conditional recommendations should be implemented through phased roll-out, starting with high-burden regions and referral centres. Pilot programmes can assess feasibility and refine protocols before national scale-up. Decision-support tools, such as algorithms and flow charts, should help clinicians interpret conditional recommendations in real-world settings, with clear triggers for escalation.

6.3 Handling "No recommendations"

Two areas lack sufficient evidence for a formal recommendation (i.e. routine PFT and echocardiogram screening for asymptomatic children). This advice is given for cases when it was not possible to make a recommendation:

- end-users should understand that an absence of recommendation does *not* imply prohibition, but rather reflects uncertainty;
- clinical judgement and local protocols should guide practice where evidence is evolving; and
- end-users should document practices and outcomes to inform future updates.

6.4 Specific recommendations considerations

- **Diagnostic POCTs:** Ensure procurement and training for frontline workers; integrate into IMCI clinical guidelines *(19)* and newborn screening programmes where feasible.
- **Antibiotic prophylaxis:** Align with immunization schedules; monitor antimicrobial resistance.
- **Hydroxyurea:** Establish dosing protocols, monitoring systems and laboratory capacity for safety checks.
- **Pain management:** Provide opioid stewardship training; ensure access to essential medicines.
- **Stroke prevention:** Strengthen TCD screening capacity; prioritize transfusion services in referral centres.
- **ACS:** Develop rapid response protocols for antibiotics and transfusion.

6.5 Conclusion

Successful implementation of these recommendations requires coordinated action among governments, health professionals, patient groups and partners. Clear communication of the rationale behind the conditional recommendations and areas with no formal recommendation is critical to avoid misinterpretation.

Stakeholder engagement, resource mobilization and accountability mechanisms should be embedded in national plans to ensure that these recommendations translate into equitable and sustainable improvements in care for children and adolescents living with SCD.

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Annex 1. Prioritized PICO questions on the clinical management of children and adolescents with SCD

1. In children aged 0–19 years at primary care facilities (i.e. without access to laboratory facilities), which point-of-care tests should be used to diagnose SCD?

Population	
Children and adolescents aged <19 years	
Intervention	**Comparator**
• Any point-of-care tests	• Haemoglobin electrophoresis
Outcomes	
• Sensitivity and specificity • Positive predictive value • Negative predictive value	• Mortality • Morbidity

2. In children age 0–5 years with SCD who have received previous pneumococcal conjugate vaccine (PCV), should antibiotic prophylaxis be initiated to prevent pneumococcal infection?

Population	
Children aged <5 years of age with SCD who have received PCV vaccination	
Intervention	**Comparator**
• Prophylaxis penicillin (oral or intramuscular (IM))	• No antibiotic prophylaxis
Outcomes	
• Invasive pneumococcal infection (i.e. pneumonia, sepsis, meningitis) • Mortality • Adverse events	• Hospital readmissions • Antibiotic resistance

3. In children aged older than 5 years with SCD, should antibiotic prophylaxis be used in preventing pneumococcal infection?

Population	
Children aged >5 years with SCD	
Intervention	**Comparator**
• Prophylaxis penicillin (oral or IM)	• No antibiotic prophylaxis • Nonpharmacological care/other prevention measures
Outcomes	
• Invasive pneumococcal infection (i.e. pneumonia, sepsis, meningitis) • Mortality • Adverse events	• Hospital readmissions • Antibiotic resistance

4. In children and adolescents (aged 0–19 years) with SCD, should penicillin antibiotics versus other antibiotics be used?

Population	
Children and adolescents aged <19 years with SCD	
Intervention	**Comparator**
• Prophylaxis penicillin (oral or IM)	• Non-penicillin antibiotics
Outcomes	
• Invasive pneumococcal infection (i.e. pneumonia, sepsis, meningitis) • Mortality	• Adverse events • Hospital readmissions • Antibiotic resistance

5. Should hydroxyurea versus no hydroxyurea be used in the management of SCD in children and adolescents aged 0–19 years regardless of clinical severity?

Population	
Children and adolescents aged <19 years with SCD	
Intervention	**Comparator**
• Hydroxyurea	• No hydroxyurea
Outcomes	
• Haemoglobin levels • Life-threatening illnesses • Acute care-seeking episodes • Hospitalization • Blood transfusions	• Acute complications: painful crises, dactylitis, acute chest syndrome, anaemia • Long-term complications: e.g. pulmonary hypertension, avascular necrosis • Adverse events (toxicity, long-term safety)

6. In children and adolescents aged 0–19 years with SCD, should non-steroidal inflammatory drugs (NSAIDs) alone versus opioids alone be used for the management of acute pain?

Population	
Children and adolescents aged <19 years with SCD and acute pain	
Intervention	**Comparator**
• NSAIDs	• Opioids
Outcomes	
• Achievement of pain control • Time to pain resolution (objective by use of pain scores)	• Patient satisfaction • Adverse events (including safety for long-term use)

7. In children and adolescents aged 0–19 years with SCD, should NSAIDs and opioids versus opioids alone be used for the management of acute pain?

Population	
Children and adolescents aged <19 years with SCD and acute pain	
Intervention	**Comparator**
• NSAIDs + opioids	• Opioids
Outcomes	
• Achievement of pain control • Time to pain resolution (objective by use of pain scores)	• Patient satisfaction • Adverse events (including safety for long-term use)

8. In children and adolescents aged 0–19 years with SCD, should paracetamol plus opioids versus opioids alone be used for the management of acute pain?

Population	
Children and adolescents aged <19 years with SCD and acute pain	
Intervention	**Comparator**
• Paracetamol	• Opioids
Outcomes	
• Achievement of pain control • Time to pain resolution (objective by use of pain scores)	• Patient satisfaction • Adverse events (including safety for long-term use)

9. In children and adolescents aged 0–19 years with sickle-cell anaemia, should regular blood transfusion therapy versus no transfusions to suppress haemoglobin S levels be used for the treatment of recurrent acute pain and/or chronic pain to improve clinical outcomes?

Population	
Children and adolescents aged <19 years with SCD and acute pain	
Intervention	**Comparator**
• Paracetamol	• Opioids
Outcomes	
• Achievement of pain control • Time to pain resolution (objective by use of pain scores)	• Patient satisfaction • Adverse events (including safety for long-term use)

10. In children and adolescents aged 0–19 years with SCD and acute chest syndrome, should antibiotics be given in addition to standard therapeutic and supportive intervention to improve clinical outcome?

Population	
Children and adolescents aged <19 years with SCD and acute chest syndrome	
Intervention	**Comparator**
• Antibiotics + standard therapeutic and supportive interventions	• Standard therapeutic and supportive interventions only
Outcomes	
• Early resolution of signs and symptoms • Improved clinical outcomes • Reduced hospital stay	• Prevention of recurrence • Mortality • Adverse events

11. In children and adolescents aged 0–19 years with SCD, should blood transfusion in combination with other standard therapeutic interventions versus standard therapeutic interventions alone be used for the treatment of suspected acute chest syndrome to improve clinical outcomes?

Population	
Children and adolescents aged <19 years with SCD and acute chest syndrome	
Intervention	**Comparator**
• Blood transfusion + standard therapeutic interventions	• Standard therapeutic interventions alone
Outcomes	
• Improved clinical outcomes including reduced hospital stay, pain, • Mortality	• Adverse events including transfusion iron overload, haemolytic transfusion reactions

12. In children and adolescents aged 0–19 years with SCD, and suspected acute symptomatic stroke, should exchange transfusion versus simple blood transfusion be used for treatment to improve clinical outcomes?

Population	
Children and adolescents aged <19 years with SCD and suspected acute symptomatic stroke	
Intervention	**Comparator**
• Exchange transfusion	• Simple blood transfusion
Outcomes	
• Secondary incidences/stroke recurrence • Better clinical outcome	• Reduced hospitalization • Mortality

13. In children and adolescents aged 0–19 years with SCD with history of stroke, should hydroxyurea therapy alone versus regular RBC transfusion plus hydroxyurea be used to prevent secondary strokes and improve clinical outcomes?

Population	
Children and adolescents aged <19 years with SCD and history of stroke	
Intervention	**Comparator**
• Hydroxyurea plus blood transfusion	• Hydroxyurea therapy alone
Outcomes	
• Secondary incidences/stroke recurrence • Reduced hospitalization	• Total adverse events

14. In children and adolescents aged 0–19 years with SCD, should routine pulmonary function testing versus no routine pulmonary function testing be used?

Population	
Children and adolescents aged <19 years with SCD	
Intervention	**Comparator**
• Periodic routine pulmonary function test screening	• Standard care (screening only when clinically indicated)
Outcomes	
• Early detection of pulmonary hypertension complications	• Unnecessary medical interventions • Mortality

15. In children and adolescents aged 0–19 years with SCD and no symptoms of pulmonary hypertension, should routine echocardiogram screening be performed or no routine echocardiography to identify pulmonary hypertension?

Population	
Children and adolescents aged <19 years with asymptomatic SCD	
Intervention	**Comparator**
• Periodic routine screening echocardiography	• Standard care/no routine screening
Outcomes	
• Early identification of pulmonary hypertension • Improvement clinical outcomes	• Mortality • Morbidity

16. In children and adolescents aged 0–19 years with SCA, should annual screening with transcranial Doppler (TCD) ultrasound or no annual screening be used to prevent stroke?

Population	
Children and adolescents aged <19 years with SCA	
Intervention	**Comparator**
• Annual TCD screening	• No annual screening
Outcomes	
• Stroke • Recurrent stroke	• Cognitive impairment • Quality of life

Annex 2. Management of conflicts of interest for the Guideline Development Group

In accordance with WHO policies and procedures for guideline development, all members of the Guideline Development Group (GDG) were required to declare any potential conflicts of interest prior to their involvement. This was done through the completion and electronic submission of the standard WHO Declaration of Interests (DOI) form.

In addition, all GDG members, methodologists and external reviewers signed confidentiality agreements to ensure the integrity and impartiality of the guideline development process.

All submitted DOI forms were reviewed by the WHO Secretariat. Any declared interests were assessed and managed in line with the procedures outlined in the *WHO handbook for guideline development*[1] and WHO's Declarations of interests for WHO experts.[2] Where a declared interest was considered potentially significant, appropriate measures were taken. These included conditional participation, partial exclusion from specific discussions or full exclusion from the guideline process, depending on the nature and extent of the interest.

At the beginning of each GDG meeting, participants were asked to declare any new or updated interests. In cases where a GDG member had contributed to a study that informed the evidence for a specific recommendation, that member was recused from the relevant discussions and decision-making, as documented in the meeting records.

Table A1.1. GDG members, affiliations, locations and areas of expertise

Name	Affiliation	WHO Region	Expertise
Mohamed Ahmed Abdullah	University of Khartoum, Khartoum, Sudan	Regional Office for the Eastern Mediterranean	Paediatric endocrinologist
Adekunle Adekile	Kuwait University, Kuwait City, Kuwait	Regional Office for the Eastern Mediterranean	Paediatric haematologist and specialist in sickle-cell disorders
Shams El Arifeen[3]	International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh	Regional Office for South-East Asia	Paediatric infectious diseases

1 WHO handbook for guideline development. Geneva: World Health Organization; 2014 (https://iris.who.int/handle/10665/145714).
2 Declaration of interests for WHO experts, https://www.who.int/publications/m/item/declaration-of-interests-for-who-experts.
3 Shams El Arifeen and Michael (Mike) English chaired the GDG meetings.

Uma Athale	McMaster University, Hamilton, Canada	Regional Office for the Americas	Paediatric haematology/ oncology
Hesham Ben Masaud	General Practice Council, Libyan Board of Medical Specialties, Tripoli, Libya	Regional Office for the Eastern Mediterranean	Paediatric programme specialist
Gillian Birchwood	The Queen Elizabeth Hospital, Bridgetown, Barbados	Regional Office for the Americas	Neonatologist
Trevor Duke	University of Melbourne, Faculty of Medicine, Dentistry and Health Sciences, Melbourne, Australia	Regional Office for the Western Pacific	Intensive care, oxygen systems and neonatologist
Michael (Mike) English[3]	University of Oxford, Oxford, United Kingdom of Great Britain and Northern Ireland	Regional Office for Europe	Paediatrics and child health; quality of care
Jane Hankins	St. Jude Children's Research Hospital, Tennessee, United States of America (USA)	Regional Office for the Americas	Haematologist and sickle-cell disease specialist
Grace Irimu	University of Nairobi, Nairobi Kenya	Regional Office for Africa	Neonatology; paediatric quality of care
Phillip Kasirye	Makerere University College of Health Sciences, Kampala, Uganda	Regional Office for Africa	Paediatric haematologist; sickle-cell disease
Shanzida Khatun	National Institute of Advanced Nursing Education and Research, Dhaka, Bangladesh	Regional Office for South-East Asia	Child health nursing
Ajay Khera	Engender Health, New Delhi, India	Regional Office for South-East Asia	Community and gender perspective

Olga Komarova	National Medical Research Center of Children's Health, Moscow, Russian Federation	Regional Office for Europe	Paediatric quality of care, adolescent health
Ida Safitri Laksono	Universitas Gadjah Mada, Yogyakarta, Indonesia	Regional Office for South-East Asia	Paediatric infectious disease, dengue
Rakesh Lodha	All India Institute of Medical Sciences, New Delhi, India	Regional Office for South-East Asia	Paediatric intensive care, pulmonology and infectious diseases
Julie Makani	Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania	Regional Office for Africa	Haematologist, blood transfusion and sickle-cell disease specialist
Refiloe Masekela	University of KwaZulu Natal, Durban, South Africa	Regional Office for Africa	Paediatric pulmonologist
Hilda Mujuru	University of Zimbabwe, Harare, Zimbabwe	Regional Office for Africa	Paediatric infectious diseases – HIV, Integrated Management for Newborn and Childhood Illnesses (IMNCI)
Mary Paiva	Buka General Hospital, National Department of Health), Buka, Autonomous Region of Bougainville, Papua New Guinea	Regional Office for the Western Pacific	General paediatrics, community, social paediatrics, district-level rural health services
Abdulkarim Rasa'a	Faculty of Medicine Sana'a University, Sana'a, Yemen	Regional Office for the Eastern Mediterranean	Paediatric infectious disease
Sergey Sargsyan	Arabkir Medical Centre. Yerevan State Medical University, Yerevan, Armenia	Regional Office for Europe	Paediatrics and adolescent preventive medicine

Dheeraj Shah	University College of Medical Sciences and GTB Hospital, New Delhi, India	Regional Office for South-East Asia	Paediatric gastroenterology and nutrition
Gezahegn Nekatibeb Techane	Debre Berhan University, Debre Birhan, Ethiopia	Regional Office for Africa	General paediatrician; paediatric quality of care specialist
Leon Tshilolo	Université Officielle de Mbujimayi, Kinshasa, Democratic Republic of the Congo	Regional Office for Africa	Paediatric haematologist/sickle-cell disease specialist
Dai Yaohua	Capital Institute of Paediatrics, Beijing, China	Regional Office for the Western Pacific	Child health nutrition, early childhood development

Table A1.2. Summary and managements of the declared interests of the GDG members

Name	Declared interest(s)	Management of conflict(s) of interest
Mohamed Ahmed Abdullah	None declared	
Adekunle Adekile	None declared	
Shams El Arifeen	Yes	The declared intellectual conflict of interest but was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility
Uma Athale	None declared	
Hesham Ben Masaud	None declared	
Gillian Birchwood	None declared	
Trevor Duke	None declared	
Michael (Mike) English	Yes	The declared intellectual conflict of interest but was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility
Grace Irimu	None declared	Not applicable

Jane Hankins	Yes	She was recused from a PICO question in which she was a principal investigator on one of the studies that informed the recommendation (regular blood transfusion in the management of acute chest syndrome). The other declared intellectual conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility
Phillip Kasirye	None declared	
Shanzida Khatun	None declared	
Ajay Khera	None declared	
Olga Komarova	None declared	
Ida Safitri Laksono	None declared	
Rakesh Lodha	None declared	
Julie Makani	None declared	
Refiloe Masekela	None declared	
Hilda Mujuru	None declared	
Mary Paiva	None declared	
Abdulkarim Rasa'a	None declared	
Sergey Sargsyan	None declared	
Dheeraj Shah	None declared	
Gezahegn Nekatibeb Techane	None declared	
Leon Tshilolo	Yes	He was recused from a PICO question in which he was a principal investigator on one of the studies that informed the recommendation (PICO 5 on hydroxyurea in the SCD guidelines). The other declared intellectual conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility
Dai Yaohua	None declared	

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