SICKLE

WHO SICKLE Package of Interventions for Sickle Cell Disease Management

Comprehensive care

Module 3

World Health Organization
African Region

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Comprehensive care Module 3

Noncommunicable Diseases (UCN) Cluster
WHO Regional Office for Africa
2024

WHO SICKLE package of interventions for sickle-cell disease management: key characteristics of a center of excellence: Module 4

WHO:AFRO/UCN:2024-02

Suggested citation. WHO SICKLE package of interventions for sickle-cell disease management: strategic guidance framework: Module 1. Brazzaville: WHO African Region, 2024. Licence: CC BY-NC-SA 3.0 IGO.

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

Designed in Brazzaville, Republic of Congo

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Acknowledgments

The development of this manual was led by Dr. Prebo Barango, Dr. Kouamivi Agboyibor, and Dr Kofi Nyarko, Regional Advisers for Noncommunicable Diseases diseases (NCDs) at the), WHO Regional Office for Africa.

The manual was prepared under the general guidance of Dr. Benido Impouma, Director of Universal Coverage, Communicable and Noncommunicable Diseases (UCN), and Prof. Jean-Marie Dangou, Coordinator of the Noncommunicable Diseases Programme at the WHO Regional Office for Africa.Benido Impouma, Director, Universal Coverage, Communicable and Noncommunicable and Diseases (UCN) and Prof. Jean-Marie Dangou, Coordinator of the Noncommunicable and Diseases Programme of WHO Regional Office for Africa.

We extend our heartfelt thanks to the international experts who were instrumental in the initial drafting of the manual. Special recognition goes to Professor Adekunle Adekile of Kuwait University (Consultant and Convener) and Dr. Olivat Rakoto Alson of Madagascar, who developed the first drafts of the Guidance Framework for Sickle Cell Disease Management (Module 1) and the Harmonized Guide for Sickle Cell Disease Management in Africa (Modules 2 to 6), respectively.

We are also deeply grateful to all the experts in the fields of Sickle Cell Disease, hematology, pediatrics, and primary health care who contributed to the drafting of this manual. Special thanks are due to:

Professor Baba Inusa (St. Thomas' Hospital, London, UK), Professor Ibrahima Diagne (Gaston Berger University, Saint-Louis, Senegal), Professor Isaac Odame (Sick Kids Hospital, Toronto, Canada), Professor Julie Makani (Muhimbili University of Health Science, United Republic of Tanzania), Professor Leon Tshilolo (CEFA-Centre Hopitalier, Monkole, Kinshasa, DRC), Professor Obiageli Nnodu (University of Abuja, Nigeria), Professor Eleonore Kafando (Burkina Faso), Professor Eric Adéhossi (Niger), Dr. Boubacari Ali Toure (Mali), Dr. Amadou N'Diaye (Mauritania), Professor Indou Deme-Ly (Center of Reference for Sickle Cell Disease, Dakar, Senegal), Dr. Paulin K. Somda (Burkina Faso), Dr. Foureratou Issoufou (Center of Reference for Sickle Cell Disease, Niamey, Niger), Dr. Uma Athle , Dr. Wilson Were, M. Ombeni Idassi (USA, St. Jude Children's Research Hospital), Dr. La'Ron Browne (USA, St. Jude Children's Research Hospital), Dr. Uma Athale(Canada, St. Jude Children's Research Hospital), Dr. Amadou Djibrilla Almoustapha (Hematology/Sickle

Cell Disease, Niger), Dr. Kwaku Marfo (Sickle Cell Disease/Hemoglobinopathies, USA), Dr. Issifou Yaya (Public Health Expert, France), Mwashungi Ally (Lecturer and Hematologist, Muhimbili Hospital, Tanzania), Maureen Memwa Achebe (Harvard University, USA), Agbeille Mohamed Falilatou (Pediatrician/Hematology, Benin).

We are also deeply grateful for Expert' from "GRAD 6 (Réseau d'experts issus de 6 pays : Burkina-Faso, Madagascar, Mali, Mauritanie, Niger et Sénégal, mobilisé pour lutter contre la drépanocytose et renforcer les partenariats entre professionnels de santé en Afrique) ", "Sickle Pan-African Research Consortium (SPARCO)" and "Sickle Cell Pan African Network (SPAN)" for all the ressources documentaires.

We would also like to thank the following individuals who reviewed the content of this manual:
Dr Janet Kayita, Dr Assumpta W. Muriithi, Dr Dorothy Achu, Dr Bridget Farham, Dr Akpaka Kalu, Dr Lwarence kazembe, Dr Charles Shey Umary Wiysonge, Akudo Ikpeazu.

Finally, we acknowledge the valuable contributions of WHO staff members from headquarters and the regional office:
Dr Sharon Kakpambwe, Dr Isimouha Dille, Dr Ould Sidi Mohamed Mohamed, Dr Joseph Mogga, Dr Joseph Mwangi, Dr Joana Ansong.

The WHO Regional Office for Africa warmly acknowledges the financial support provided by the Government of the Principality of Monaco and the encouragement of Mrs. Anne Poyard, Deputy Director for Monaco. This gratitude extends to other partners supporting the NCDs programme, and this work. We recognize the critical role these partners have played in the development of this comprehensive package and thank them for their continued support in the fight against sickle cell disease.

1. Screening and diagnosis

1.1 Screening

The initial diagnosis of SCD is made either as a part of neonatal screening, mass screening campaigns, intrafamilial screening or when the disease is suspected on the basis of personal or family history, or during clinical manifestations and/or complications, or during pregnancy.

When should we suspect SCD?

The three common features of SCD are anaemia, jaundice and recurrent pain. When a patient presents with any or all of the above, screening for SCD should be done. In addition, anybody presenting with complications like infections, stroke, seizure, priapism, or leg ulcers needs to be suspected of having SCD.

Evaluation and diagnosis of sickle-cell disease takes account of resources and facilities available at the various levels of care (See Table below).

Evaluation of patients with suspected SCD is based on complete blood count with examination of the blood smear, and on tests that detect the presence of haemoglobin S, which must be confirmed by haemoglobin electrophoresis or other analyses directly demonstrating abnormal haemoglobin. In all cases, all tests and investigations must be subject to current quality control regulations. Of note, the patient should Not have been transfused with red cells for at least 3 months prior to the testing for SCD.

Screening tests

- The **blood count** shows anaemia with a baseline haemoglobin level that varies from patient to patient, averaging 6-8 g/dl. The anaemia is typically hyper-regenerative, associated with high reticulocyte count.
- The blood smear reveals **sickle cells**. Specific screening tests for the presence of haemoglobin should be available at all levels of care.
    - Emmel's sickling test demonstrates in vitro the sickling of red blood cells under hypoxic conditions, indicating the presence of haemoglobin S. It uses 2% sodium metabisulfite to induce hypoxia.
    - The Itano solubility test is based on the hyposolubility of deoxygenated haemoglobin S in phosphate buffer, which precipitates in the presence of dithionite.
    - The point-of-care test (POCT) for SCD is an immunochromatographic assay identifying haemoglobin A, S, and C.

Please note that the above tests can also detect carrier status.

Confirmation tests

The results of haemoglobin electrophoresis and high-performance liquid chromatography (HPLC) are dependent on the age of the patients. The absence of normal Hb A is diagnosed, except for patients with Hb S/β^+ thalassemia.

Haemoglobin electrophoresis directly identifies haemoglobin S and confirms the diagnosis. It can be carried out using either the classic method, performed on cellulose acetate at alkaline or acidic pH, or by isoelectric focusing (IEF), in a pH gradient allowing better separation of haemoglobins, excellent for detecting abnormal haemoglobins during the neonatal period.

The following can be found only in the homozygous SS form:

- a majority of haemoglobin S (75-95%);
- haemoglobin A2 approximately normal (2- 4%);
- fetal haemoglobin or haemoglobin with variable levels (0- 20%).

In H b SC, there is approximately 50% haemoglobin C and 50% haemoglobin S.

In the case of Sβ-thalassemia double heterozygosity, there are two forms:

- Sβ0thalassemia: presence of haemoglobin S, F and A2;
- Sβ+thalassemia: presence of haemoglobin S ,F, A1 and A2.

Please refer to the Table below.

1. HPLC and capillary electrophoresis quantify with precision abnormal haemoglobin variants over the time taken to eluate.
2. Molecular biology is used to identify the mutated gene using the polymerase chain reaction (PCR) method. Hence, it can be done at any age including in utero.
3. Antenatal or in utero diagnosis of SCD;
4. PCR-based molecular diagnosis can be used as early as the eighth week of gestation.

Table 1. Resources and facilities according to care centre level

	Level I (primary care)		Level II (secondary care)	Level III (tertiary care)
	1- Health post (nurses)	2- Health centre (doctors and nurses)	3-Regional or municipal hospital	4-Reference centre, university hospital specialized care unit
Terms and conditions	Family screening (history) Clinical manifestations	Neonatal screening, Mass screening, family screening, Clinical manifestations	Neonatal screening, Community screen-ing drives, -family screening Clinical manifesta-tions	Neonatal screening, Community screening drives, family screening, Clinical manifestations
Resources	POCT	POCT Falciformation	POCT IEF Falciformation Solubility	POCT Sickling Solubility IEFHBHPLCPCR
References	Refer to Level II	Refer to Level III for confirmation	Refer to Level III for confirmation	

Table 2. Different approaches to the initial diagnosis of SCD

	Neonatal screening	Screening campaigns	Intrafamily screening	Diagnosis of clinical manifestations and/ or complications
Specific objectives	▪ Early diagnosis of SCD ▪ Early management of children with SCD	▪ Screening subjects with undiagnosed major SC syndromes ▪ Screen subjects with heterozygous hemoglobinopathies (AS, AC, Athal)	▪ Screening for undiagnosed SCD in the family ▪ Screen family members with heterozygous hemoglobinopathy (AS, AC, Athal)	▪ Diagnosing SCD in a patient with signs or complications suggestive of major SC syndrome
Terms and conditions	▪ Availability of a laboratory and methods for neonatal diagnosis of hemoglobinopathies ▪ Setting up care conditions for children with SCD	▪ Availability of screening methods (Emmel, Itano) or rapid diagnostic tests ▪ Possibility of referral to SCD care structure ▪ Access to information and genetic counselling	▪ Availability of diagnostic methods for various major SC syndromes (blood smear, EHB) ▪ Possible management of SCD ▪ Access to information and genetic counselling	

1.2 Clinical diagnosis

The clinical picture of SCD in the intercritical phase is characterized by anaemia of variable intensity and frank jaundice. Splenomegaly is most common in children under five years of age and tends to disappear after that age.

There is often a delay in staturo-ponderal development.

Vaso-occlusive crises are acute painful episodes. They are the most frequent manifestations of the disease. They may be spontaneous or triggered by:

- infection;
- dehydration;
- exposure to cold;
- intense physical effort;
- psychological stress;
- even pressurized air travel;
- a stay at altitude.

Their frequency and intensity vary from one patient to another. Vaso-occlusive crises are abdominal and/or osteoarticular in nature.

The vaso-occlusive crises stem from the obstruction of small vessels, a source of ischaemia.

Haemolysis results from the exaggerated destruction of red blood cells in a state of irreversible sickling.

Particular susceptibility to infection is partly the result of progressive **auto-splenectomy** (functional exclusion of the spleen) and reduced **phagocytic** capacity of polynuclear cells. Furthermore, deformed red blood cells are dehydrated, hyper-concentrated and hyper-aggregable. They thus increase **blood viscosity** and **stasis**, which then aggravate hypoxia and acidosis. The result is a vicious circle.

These different **vaso-occlusive, haemolytic** and **infectious** phenomena are often interlinked. They are responsible for the clinical manifestations and acute and chronic complications of SCD.

In infants aged between 6 and 18 months, bony manifestations of the **"hand-foot"** or dactylitis **syndrome** are characterized by severely painful inflammatory oedema of the backs of the hands and feet, typically bilateral and symmetrical. Low-intensity vaso-occlusive seizures may resolve spontaneously within three to four days. However, they most often evolve into more severe attacks requiring appropriate treatment.

2. Health maintenance for patients with SCD

Effective management is based on a number of principles: early diagnosis, regular follow-up, patient and family education, and multidisciplinary collaboration. It is essential that therapeutic interventions be designed according to the level of care and continually interwoven with psychosocial, physical and medical aspects, for integrated disease management. Care should be patient-and family-centred.

The universal ***neonatal screening*** strategy is strongly recommended. When neonatal screening is not available, the diagnosis of SCD must be established as early as possible as outlined in Chapter 3. Ideally, **early treatment should begin before the age of 4 months**, to improve quality of life and reduce SCD-related infant and childhood mortality.

2.1 Health maintenance in steady state

Every patient diagnosed with a major sickle-cell syndrome must receive regular follow-up, in which information, education and communication (IEC) play a key role.

Information is generally provided (at all levels of care) on:

- how the disease is transmitted
- clinical manifestations
- complications
- disease-modifying therapies (such as hydroxyurea)
- and above all, preventive measures.

Follow-up should be regular, every 3 to 4 months, depending on the patient's clinical condition. Perform the following actions:

- assess the general and nutritional condition
- check growth and pubertal development
- assess spleen size
- provide immunization and extended immunization (Level 1)
- carry out complete blood count, including reticulocyte count, (Level I)
- In older patients, carry out abdominal ultrasound, pulmonary function tests, renal functions, urinary microalbumin/creatinine ratio, ophthalmology check-up (Level II/III).

Age-appropriate frequency of monitoring:

Age (years)	<2	]2–15[	>15
Frequency (months)	2	3–4	6

Baseline laboratory tests to be done as below:

- Blood grouping (Level I) with extended red cell phenotype if possible, Level II - III
- Haemoglobin electrophoresis with determination of the various fractions, Level II-III
- Transfusion record with complete red cell phenotype and cross match, Level II-III
- Viral serologies (HIV, hepatitis B and C) at baseline and prior to blood transfusion, Level II-III
- Other tests: transcranial Doppler (TCD) annually, abdominal ultrasound annually, serum ferritin as needed Level II-III.

Parents are advised to take prophylactic measures to mitigate the disease and improve quality of life. These measures include:

- nutrition
- hydration
- hygiene
- regular clinic visits
- protection against weather extremes.

Table 3. Health maintenance according to levels of care

	I		II	III
Behavioural change communication				
Complete blood count (CBC) and reticulocyte count				
GsRH				
Extended phenotype				
Haemoglobin electrophoresis				
Irregular erythrocyte antibodies				
Serological test (HIV, hepatitis B and C)				
Blood transfusion				
Abdominal ultrasound				
Ferritinaemia, LDH, BT and BC and transaminase				
Transcranial Doppler (TCD)				
Bone X-ray				
Ophthalmological examination				
Renal assessment (uraemia and creatinaemia and microalbuminuria, ECBU)				
Lungs X-ray				
Echocardiography				
Regular monitoring every 3 to 4 months (general and nutritional condition, height and weight development, jaundice, pallor, spleen)				

Preventive measures (primary and secondary)				
Prevention of infections (good oral hygiene, good body hygiene, vaccination, antibiotic prophylaxis, antimalaria prophylaxis and systematic deworming)				
Prevention of worsening of anaemia (folic acid supplementation)				
Prevention of VOC				
Red cell exchange transfusion				
Erythropheresis				
Therapeutic education				

2.2 General preventive measures

For most patients, prevention is the only way to combat acute and chronic complications of SCD. It is based on preventive measures against:

- infections,
- worsening of anaemia
- vaso-occlusive crisis
- stroke.

*Can be provided at all levels of care

Infection prevention

In addition to general principles of good oral hygiene (dental care) and bodily hygiene (cleanliness of skin and hair, hands and feet, clothes, home) and good nutrition (healthy, high-quality food), specific preventive measures for patients with SCD include:

- Extended immunization (in addition to routine vaccination) against encapsulated organisms (Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae B, Salmonella typhi) and hepatitis B; Level I-II- III
- Antibiotic prophylaxis; Level I-II-III
  - Antibiotic prophylaxis for up to five years with penicillin V or alternate if patient is allergic to penicillin.
- Malaria prevention prophylaxis; Level I-II-III
  - Technique: use of mosquito netting, cleanliness of the environment, use of insecticides
  - Chemoprophylaxis according to local guidelines

- Malaria immunization, if available.

- Systematic deworming (antihelminthics); Level I-II-III
  - Every 3 months for under-five children and every 6 months for over-five children.

Prevention of worsening anaemia

This involves supplementing patients with folic acid at a dose of 5 mg a day for 10 to 20 days a month and correcting any iron deficiency; Level I-II-III.

Preventing vaso-occlusive crisis

- It relies on good education to avoid all circumstances likely to trigger or aggravate these episodes; Level I-II-III.

- The aim is to prevent:
  - hypoxia by avoiding strenuous physical effort, spending time at high altitude, confined atmospheres, extremes of temperatures, stress and any situation that causes vasoconstriction;
  - dehydration by drinking plenty of water and avoiding exposure to heat or sudden temperature changes, seeking medical attention in the event of significant water loss (namely hyperhidrosis, diarrhoea, vomiting or fever).

- A systematic clinical examination should be carried out prior to air travel, and plenty of water should be drunk before and during the flight. The same applies to preparation for a long, arduous road trip. Leg stretching sessions should be carried out to avoid sitting for too long. Level II-III.

3. Management of complications

3.1 Acute complications

The aim of this chapter is to provide information for emergency treatment of acute complications of sickle-cell disease and to detect and treat chronic complications at an early stage, in order to improve the patient's quality of life and life expectancy.

Sickle-cell syndromes are characterized by (critical alternating) periods of vaso-occlusive crises and a basal state, and can involve both acute and chronic complications.

3.1.1 Treatment of vaso-occlusive crises

Pain or vaso-occlusive crises are the most frequent reason for hospital visits for a sickle-cell patient. Painful episodes primarily occur within the long bones of the body.

The management of pain depends on symptom management; however, prevention of pain episodes should also be considered, including the use of disease-modifying agents such as hydroxyurea which can aid in decreasing frequency of pain crises.

Prevention relies on proper education on the precipitating factors for vaso-occlusive crises (dehydration, change in altitude, extremes in temperature, infections, physical and psychological stress). While most painful episodes occur within the long bones, it is important to perform a thorough clinical examination with adequate assessment of pain or the management of a pain crisis. The visual analogue scale (VAS, see Annex) is widely used as a pain assessment instrument.

If pain is associated with the following signs and symptoms: fever, shortness of breath, severe headache, vomiting, or if the pain is different from the patient's baseline sickle-cell pain, the patient should be assessed immediately at the nearest health centre.

Treatment should be individualized and tailored to the patient. Base analgesic selection is dependent on pain assessment and associated symptoms. The patient's own knowledge of effective agents and doses, as well as past experience with side effects should be taken into consideration.

Treatment is symptomatic and can be managed across the different levels of the health system, including patients with mild pain that can be managed at home with oral hydration, oral analgesia and warm applications to affected areas of pain. Thermometers should also be provided to caregivers and patients to ensure there is no fever during a pain crisis.

The three WHO treatment strategies should be used for managing pain in adults in addition to the WHO two-step strategy that should be utilized for children. Please refer to the Annex for WHO hydration recommendations for both children and adults.

Analgesics: Please refer to the Annex – WHO ladder.

- Hydration: orally or intravenously, at the rate prescribed by the WHO guidelines. Please refer to the Annex.

3.1.2 Acute management

In patients presenting with acute pain crisis at any health centre, there should be rapid assessment of the patient's recent analgesic use (opioid and no opioid), followed by rapid administration of initial analgesic therapy within 30 minutes of triage or within 60 minutes of registration. Patients should be reassessed and if pain persists, there should be re-administration of opioids if necessary for continued severe pain until pain is under control per patient report. Adjustment of medications should be considered depending on the side effects.

Chronic pain can occur in a subset of patients with SCD and the management requires a multidisciplinary approach.

Table 4. Chronic pain management according to level of care

Care levels				
	I a	Ib	II	III
Actions to be performed				
Physical examination				
Evaluate for areas of pain				
Use of visual analogue scale for pain score				
Investigations				
Rapid diagnosis of sickle cell via POCT or Emmel (sickling) test				
Haemoglobin electrophoresis				
Treatment				
Oral hydration for mild pain				
Oral analgesia for mild pain episodes				
IV hydration recommended for patients with moderate to severe pain episodes and failure to tolerate fluids				
IV analgesia if pain is severe, persistent or recurrent				
Refer to Level 1b/II facilities for persistent and moderate to severe pain				
Please refer to Annex for types and routes of analgesia				

3.2 Infection

Patients with SCD are at risk of overwhelming septicaemia with encapsulated organisms due to loss of splenic function.

There are many and varying types of infectious processes occurring in SCD including pneumonia, meningitis, septicaemia, and osteoarticular infections. Other infectious processes should also be evaluated, such as parasitic infections, particularly malaria in addition to viral infections.

Initial antibiotic treatment should always take into account the most common pathogens within a region or area. However, infectious causes such as Streptococcus pneumonia < Hemophilus influenza type B, salmonella should be considered first. Specifically, osteoarticular infections are mainly due to Staphylococcus aureus and salmonella.

Infection and acute anaemia are the most common causes of death in children with SCD, particularly in the under-five-year age group, hence any patient presenting with signs of infection should be evaluated and treated urgently. Any patient with SCD presenting with a fever higher than 38.5 Celsius (C) and or 101.5 Fahrenheit (F) should seek immediate medical management at the nearest hospital.

Patients should have a complete history and physical examination performed by health personnel, with the following basic tests performed, including peripheral IV insertion for essential treatment and medication.

If a facility is unable to perform any of these tests, the patient should be referred immediately to a referral or specialist hospital for further management and care.

Table 5. Physical examination, investigation and treatment for infections

Care levels				
	Ia	Ib	II	III
Actions to be performed				
Physical examination				
Temperature testing with thermometer				
Check for signs of irritability				
Check for signs of dehydration				
Check for signs of meningism				
Evaluate for any chest symptoms				
Investigations				
Malaria rapid diagnostic testing				
Rapid dengue testing				
Urinalysis				
Full blood count or complete blood count				
Blood culture				
Procalcitonin				
Chest X-ray				
■ Other lab or diagnostic investigations based on clinical examination				
■ Rapid diagnosis of sickle cell via POCT or Emmel (sickling) test				
■ Haemoglobin electrophoresis				

Care levels				
	Ia	Ib	II	III
Treatment				
■ Initial broad spectrum antibiotics to cover the most common pathogens in the area				
Antipyretics				
Oral antibiotics				
IV antibiotics broad spectrum				
Antimalarial treatment if malaria test is positive				
Hospitalize in case of severe infection				
Next level of care referral to consider				
If high or persistent fever (more than three days)				
If severe infection (meningitis, severe pneumonia, septicaemia, osteoarticular infection or persistence of signs after initial treatment)				
• Other considerations				
■ Search for and treat any associated acute complication (hydration, transfusion)				
■ Recover nutrition possibly by protein and vitamin supplementation				

3.3 Severe acute anaemia

Severe acute anaemia is characterized by a rapid/abrupt worsening of clinical anaemia or a drop of at least two (2) grams in the steady haemoglobin with the presence of one or more of the following clinical signs: unusual fatigue, increased pallor, shortness of breath at rest, palpitations, and tachycardia.

Causes of severe acute anaemia include the following:

- Haemolysis that is characterized by increased jaundice and worsening signs of anaemia. Infections, particularly malaria and sepsis, are often the triggering factors.

- Acute splenic sequestration is a life-threatening emergency of SCD characterized by severe anaemia, significant increasing size of the spleen, and an elevated reticulocyte count. Patients with suspected or confirmed splenic sequestration should be referred to the nearest next level facility that has blood transfusion capabilities.
- Hepatic sequestration is a life-threatening emergency of sickle-cell disease characterized by severe anaemia and significant increasing size of the liver. Patients with suspected or confirmed liver sequestration should be referred to the nearest next level facility that has blood transfusion capabilities
- Aplastic crisis is characterized by severe anaemia and low reticulocyte count with no change in spleen size. It is usually secondary to erythrovirus (parvovirus) B19 infection.

Table 6. Physical examination, investigation and treatment for severe acute anaemia

Care levels				
	Ia	Ib	II	III
Actions to be taken				
Physical examination				
Fatigue or decreased energy from baseline				
Increased pallor				
Shortness of breath at rest				
Palpitations				
Tachycardia or elevated heart rate				
Evaluate for spleen size				
Evaluate for liver size				
Investigations				
Complete blood count/full blood count				
▪ Reticulocyte count				
Malaria rapid diagnostic test				

Care levels				
	Ia	Ib	II	III
Parvovirus PCR or serology testing if available				
Blood culture				
Rapid diagnosis of sickle cell via POCT or Emmel (sickling) test				
Haemoglobin Electrophoresis				
Treatment				
Refer to health centre or hospital				
Ensure IVA				
Transfusions				
Simple transfusion				
■ 10 ml/kg with repeat CBC after transfusion in splenic and liver sequestration (5 ml/kg for children)				
■ 10 ml/kg if no concern for splenic/ liver sequestration (5 ml/kg for children)				
■ Consider splenectomy if splenic sequestration is recurrent				
Post splenectomy				
Lifelong prophylaxis for encapsulated Abx after splenectomy.				

3.4 Vaso-occlusive complications

3.4.1 Stroke

Stroke is a life threatening and debilitating complication of SCD affecting all age groups of sickle-cell patients including infants. There are two types that can occur: ischaemic stroke characterized by obstruction of vessels, and haemorrhagic stroke caused by rupture of neo-vessels. All patients with suspicion of, or confirmed stroke should be referred immediately to a specialized or Level III centre.

Table 7. Physical examination, investigation and treatment of stroke

Care levels				
	Ia	!b	II	III
Actions to be taken				
Physical examination				
Altered mental status				
Seizures				
Sensory or motor deficits				
Receptive aphasia				
Expressive aphasia				
Cranial nerve deficit				
Investigations				
Complete blood count/full blood count				
Haemoglobin ID				
Rapid diagnosis of sickle cell via POCT or Emmel (sickling) test				
Haemoglobin electrophoresis				
CT scan to assess for intracranial bleeding				
Brain MRI/MRA				
Treatment				
Immediate referral to Level III				
Transfusion is recommended				
Simple transfusion to goal of 10 g/dL				
Exchange transfusion with goal to reduce HbS fraction to < 30%				
Post-stroke diagnosis				
> Set up a monthly transfusion programme if available/schedule > Start treatment with hydroxycarbamide (hydroxyurea)/Annex >Discuss with the family the possibility of access to bone marrow transplants				
> Enrolment in rehabilitation programme.				

3.4.2 Acute chest syndrome (ACS)

ACS is a life-threatening medical emergency and one of the main causes of death in sickle-cell patients. Symptoms can present with fever, hypoxia below 92% on pulse oximeter, cough, chest pain or shortness of breath and new infiltrates on chest X-ray.

The causes of ACS are multifactorial and can be due to infections, sickling of red blood cells in the lungs and/or blood clots.

Patients with suspected diagnosis of ACS should be referred immediately to a specialized facility or Level II or III centre for management.

Table 8. Physical examination, investigation and treatment of acute chest syndrome

Care level				
	Ia	Ib	II	III
Actions to be taken				
Physical examination				
Cough				
Shortness of breath				
Evaluate for fever				
Hypoxia < 92 %				
Investigation				
Inserting a venous line				
Chest XR to determine new infiltrate on XR				
Blood culture				
CBC				
Procalcitonin				
Rapid diagnosis of sickle cell via POCT or Emmel (sickling) test				
Haemoglobin electrophoresis				
Treatment				
Pain management				

Care level				
	Ia	Ib	II	III
Antibiotics therapy irrespective of bacterial growth				
Oral amoxicillin (3 g/d in adults, 100mg/kg/d in children) if no IV antibiotics available				
Oral macrolides for atypical pneumonia				
IV cephalosporins				
Oral macrolides for atypical pneumonia				
Refer to Level II/III				
Hydrate with caution: reduce the volume indicated for hydration by 1/4 or 1/2 / Annex				
Oxygen if patient is hypoxic based on criteria described above				
Transfusion				
Simple transfusion to goal hgb of 10 g/dL				
Exchange transfusion if Hgb is 10 g/dL and if available				
Admit patient to intensive care unit				
Management for PE only if confirmed on CTPa				
Low molecular weight heparin (LMWH) or direct oral anticoagulation if PE is confirmed.				

3.4.3 Priapism

Priapism is characterized by painful, prolonged erection unrelated to sexual stimulation and is due to blood sequestration and engorgement of the corpora cavernosa. It is a medical emergency and failure to treat can lead to permanent functional sequelae with the risk of sexual impotence.

- Acute priapism that can be preceded by episodes of intermittent priapism, often unreported.
- Intermittent 'stuttering' priapism – intermittent episodes of painful erections with spontaneous resolution.

Management also includes education of parents and caregivers of males with SCD in childhood and encouraging patients to inform their caretakers and physicians when these episodes occur.

Table 9. Physical examination, investigation and management of priapism

Care level				
	Ia	Ib	II	III
Actions to be implemented				
Physical examination				
Document time of onset of symptoms				
Evaluate if this is the first-time episode				
Complete blood count/full blood count				
Reticulocyte count				
Hb S quantification/Hgb ID				
Confirm diagnosis of sickle cell with POCT or Emmel (sickling) test				
Treatment				
Encourage micturition				
Encourage ambulation/walking				
Warm baths/warm compresses				
Treating pain/Annex				
Hydration/Annex				
Sedation or anxiolytics				
Referral criteria				
If persistent for > 2 hours				
If recurrent, intermittent for > 2 hours				
Urology management at Level II and III				

Care level				
	Ia	Ib	II	III
■ Instituting urological treatment: > Drainage of the corpora cavernosa/Annex 12 > Intracavernous injection of etilefrine/Annex 13 > Corpus cavernosum bypass (on the advice of a urologist).				

3.4.4 Sickle-cell hepatopathy

"Sickle-cell hepatopathy" is an umbrella term that includes varying liver diseases encountered in patients with SCD. The pathology is diverse and is due to various insults to the liver that can occur in these patients. These include the following: intrahepatic cholestasis, choledocholithiasis and hepatic crisis.

Table 10. Physical examination, investigation and treatment of sickle-cell hepatopathy

Care Level				
	Ia	Ib	II	III
Actions to be taken				
Physical examination				
Right upper quadrant pain/discomfort				
Hepatomegaly or liver enlargement				
Worsening jaundice				
Investigations				
Insert a venous line				
Viral screen (CMV, EBV, hepatitis studies)				
Complete blood count/full blood count				

Care Level				
	Ia	Ib	II	III
Liver function enzymes/assays (LFTs)- AST/ALT/AlkPhos/GGTp				
Bilirubin levels – total bilirubin, direct bilirubin				
Abdominal US + Doppler US of the liver				
Rapid diagnosis of sickle cell via POCT or Emmel (sickling) test				
Haemoglobin electrophoresis				
Treatment				
Refer to Level II/III hospital				
Pain management				
IVA intravenous access				
IV hydration				
Transfusion (exchange or simple transfusion)				

3.4.5 Multisystem organ failure

Multisystem organ failure is a life-threatening emergency that requires aggressive symptomatic treatment involving a multidisciplinary approach. It is important to have a high index of suspicion for every patient with SCD, especially in the setting of rapid clinical deterioration and worsening renal and liver dysfunction, respiratory compromise or failure and other organ dysfunction.

Immediately contact a haematologist or SCD expert, establish central venous access and initiate a simple or exchange transfusion. All patients should be referred to and managed at a Level III medical centre.

4. Chronic complications

4.1 Leg ulcers

Leg ulcers are a highly disabling chronic complication of SCD.

They occur more frequently from adolescence onwards in severe types of SCD patients with low baseline haemoglobin. It is a manifestation of vasculopathy related to haemolysis.

It is a chronic, painful condition which has a tendency for frequent recurrence even after healing. It commonly occurs above the ankle area. Hence, it is important to undertake preventive measures to avoid its occurrence or recurrence:

- wear socks and well-fitted shoes
- use insect repellents
- treat minor trauma quickly
- avoid blood tests or IV lines in lower legs
- wear compression socks
- ensure good skin hydration in case of dryness (moisturizing cream)
- avoid even minimal trauma to the malleolar region.

Therapeutic goal:

Ensuring early and appropriate management of leg ulcers in sickle-cell patients.

Table 11. Management of leg ulcer at the various levels of care

	I		II	III
Actions to be implemented				
■ Systematic examination of the legs (malleolar regions) for early signs of skin breakdown				
Diagnosis of leg ulcers				
■ Daily dressing or every other day depending on condition (Annex 14)				
■ Recommend rest with elevation of lower limbs				
■ Give painkillers in case of pain				
■ Consider systemic antibiotics if there is suspicion of infection				
■ Refer to a dermatologist for advice				
■ Start hydroxyurea if already not on, or consider a monthly transfusion programme				
■ Discuss skin grafting with dermatologists in case of favourable evolution				
■ Consult surgery for management of ulcer (e.g. debridement) and/or skin grafting if needed				

Please refer to flow diagram outlining management of patients with leg ulcers (Annex 18).

4.2 Gallstones

Gallstones or cholelithiasis is a frequent complication that may occur as early as 5 years of age in patients with SCD. It might be asymptomatic or may present with provoked or unprovoked right upper quadrant abdominal pain. Sometimes the patient may have cholecystitis (inflammation of the gall bladder) which presents with fever, jaundice and severe abdominal pain.

Early diagnosis of cholelithiasis is important to avoid acute abdomen due to cholecystitis or obstruction of bile duct or pancreatic duct by gallstones. For early diagnosis of gallstones, it is important to evaluate and document the presence or absence of history of pain and tenderness in the right upper abdominal quadrant during every health maintenance visit, and annual abdominal ultrasound examinations from the age of 5 onwards. Presence of gall bladder sludge by the ultrasound is the earliest sign of gallstone formation and may require intervention.

Therapeutic goals:

- Early diagnosis of gallstones in patients with SCD.
- Ensuring appropriate management of gall stones in patients with SCD.

Table 12. Management of gallstones at the various levels of care

	I		II	III
Actions to be implemented				
■ Suspected gallstones in the presence of recurrent abdominal pain, especially localized to the right upper quadrant and/or persistent jaundice				
■ Institute analgesic treatment (Annex)				
■ Refer to a higher Level II or III				
■ Confirm with ultrasound Level II or III				
■ Hydrate(Annex 10)				
■ Institute antibiotics therapy if an infectious complication (e.g. cholecystitis) is suspected				

	I		II	III
■ Confirm diagnosis (abdominal ultrasound, bilirubinemia, alkaline phosphatases, transaminases)				
■ Emergency treatment of associated infectious complications (acute cholecystitis, angiocholitis, acute pancreatitis)				
■ Plan cholecystectomy, giving preference to laparoscopic approach if available and indicated				
■ Preparing for surgery/Annex 22				

Please refer to flow diagram outlining management of patients with gallstones (Annex 22).

4.3 SCD nephropathy

SCD nephropathy involves damage to the glomeruli and tubules of the kidneys. It can occur as early as the age of 8 or 10 years in children with sickle-cell disease.

It develops insidiously and is clinically asymptomatic until renal failure occurs. The appearance of microalbuminuria is the earliest detectable manifestation of sickle-cell nephropathy.

Therapeutic goals:

- Implementing effective management of sickle-cell nephropathy.

Table 13. Management of leg SCD nephropathy at the various levels of care

	I		II	III
Actions to be implemented				
■ Screen for hypertension, proteinuria and/or haematuria and signs of renal failure (oliguria, worsening anaemia, swelling)				
■ Refer to Level II for assessment				
■ Confirm diagnosis of nephropathy (clinical, proteinuria, haematuria, azotaemia, high creatinine levels or sudden increase in the creatinine level from baseline)				

	I		II	III
■ Refer to Level III if nephropathy confirmed				
■ Confirm nephropathy and diagnose renal failure (24-hour diuresis, microalbuminuria, creatinine and creatinine clearance, glomerular filtration rate)				
■ Investigate and manage hypertension				
■ Avoid contrast media, NSAIDs, nephrotoxic drugs				
■ Prescribe an angiotensin-converting enzyme inhibitor (captopril25 mg/d)				
■ Ensure proper oral hydration with alkalization when evidence of metabolic acidosis				
■ Supplement with calcium and vitamin D if needed				
■ Prescribe erythropoietin therapy for severe anaemia				
■ Draw up a transfusion programme if needed (See Annexes 6 and 7)				
■ Starting treatment with hydroxyurea (Annex 11).				

Please, refer to flow diagram outlining management of patients with SCD-related nephropathy (Annex 20).

5. Special considerations for management of SCD

5.1 Pregnancy and childbirth in women with SCD

Every pregnancy in a patient with SCD is a HIGH-RISK pregnancy which requires special attention. All pregnant women should be referred to Level II or Level III care and all deliveries should be undertaken at Level II or Level III. The onset of pregnancy in a woman with sickle-cell disease requires special attention. Pregnancy increases the risk of vaso-occlusive crises and acute complications of sickle-cell disease. SCD can induce pregnancy complications for both mother and fetus, hence these patients are at high risk, and all patients should be delivered at a high-level medical centre.

Pregnancy management requires collaboration between the haematologist, obstetrician and paediatrician.

In addition to specific obstetrical measures, special measures are required for the management of sickle-cell patients:

- Suspension of hydroxycarbamide (hydroxyurea) treatment;
- Preventive transfusion programme;
- Aspirin initiation after 12 weeks antepartum for prevention or prophylaxis for pre-eclampsia;
- Ensure prevention of dehydration, acidosis, infection;
- Ensure proper nutrition.

Optimization for birth and delivery:

- Include transfusion to a haemoglobin of 10g/dL in the peripartum period;
- Ensure an adequate pain plan;
- Require a multidisciplinary approach for timing of delivery, route of delivery, with consideration of the maternal condition and the possibilities for neonatal care.

Anaesthesia plan: give preference to locoregional anaesthesia if a caesarean section is indicated.

Postpartum management

Perform systematic newborn screening for sickle-cell disease if available. Consider use of VTE prophylaxis. Assessment of newborns for opioid withdrawal and opioid dependency.

Discharge plan:

Discuss the introduction of contraception.

Ensure continued optimization of mother and baby.

NB: Pregnancy can be properly managed in a woman with a major sickle-cell syndrome.

5.2 Reproductive health

All pregnancies in patients with SCD (both males and females) should be planned, if possible.

5.2.1 Females:

- Genetic counselling
- Contraception/type of contraception
- Stopping HU in pregnancy
- Spacing childbirths to allow for maternal recovery
- The patient, their partners and family should be educated on the complications of pregnancy for the mother and fetus.

5.2.2 Males:

- Genetic counselling
- Discussion of fertility issues (risks and benefits of HU including transient azoospermia)

- If infertility is suspected, then future work-up may be considered
- Suspension of HU three months prior to conception.

5.2.3 SCD carriers:

- Genetic counselling
- Offer intrauterine diagnosis if available.

All patients with SCD should be educated on the various contraception options and be referred to an obstetrician and gynaecologist for the management and initiation of contraception. The decision for contraception should be individualized and jointly agreed between the patient and their physician. Please refer to the Annex for types of contraception.

Perioperative and surgical considerations

Perioperative management

This depends on the type of surgery, which can be classified as minor surgery or major surgery.

Minor surgery: is usually surgery performed under local anaesthesia and does not need general anaesthesia (GA). Example of minor surgery:

- Removal of ingrown toenails
- Removal of lumps and bumps (such as lipomas)
- Sutures for open wounds.

All others are considered major surgery, especially if it requires GA, such as for:

- Cholecystectomy
- Splenectomy
- C-section
- Joint replacement.

Patients should avoid sex if they have a fever or VOC.

Please refer to flow diagram below for perioperative management of patients with SCD.

Other comorbidities that may worsen SCD-related manifestations include:

Asthma or reactive airway disease: patients with SCD have high prevalence of asthma and reactive airways disease which may worsen the pulmonary dysfunction.

Asthma is a common disease associated with acute chest syndrome (ACS) and SCD due to its high prevalence in the general population. Asthma attacks in SCD is triggered similarly by cold weather, cigarette smoke, allergies and pets. Its clinical manifestations are the same for SCD and non-SCD and include recurrent episodes of wheezing, intercostal and supraclavicular retractions, shortness of breath, a cough that is worse at night and exercise intolerance, among other

findings. These symptoms are caused by bronchial hyperresponsiveness, episodic bronchoconstriction, and acute-on-chronic inflammation. Exacerbation of asthma attacks gives rise to important mucous secretions, ventilation-perfusion mismatch and hypoxaemia. This hypoxaemia in SCD causes RBC sickling in the blood vessels, predisposing asthmatic SCD to ACS. Asthma is shown to increase twice ACS incidence in SCD. Paediatric patients with asthma have been reported to get their first ACS episode earlier than the non-asthmatic, with median age of 2.4 years versus 4.6 for the latter. Asthma is also associated with increased mortality in SCD. The treatment in asthma exacerbation is based on corticosteroids which outweigh the concern of precipitating a potential VOC. Other additional treatment options for management include supplementary oxygen therapy, inhaled short-acting β2 agonists, and intravenous magnesium sulfate for severe cases.

Adenotonsillar hypertrophy (ATH):

Adenotonsillar hypertrophy seems to be more frequent in children with SCD, and results in recurrent pharyngitis. The causes of ATH are not yet fully determined, but recurring chronic or acute inflammation have been involved, including also hyperplasty of lymphoid cells. Several hypotheses can be put forward for ATH and SCD association: compensation of splenectomy, consequence of recurrent infections of the upper airways due to failed opsonization of pathogenic bacteria; and the function of pharyngeal and palatine tonsils as hematopoietic centres due to haemolysis. ATH can lead to sleep-disordered breathing varying from snoring to obstructive sleep apnoea syndrome resulting in hypoxaemia, hypercapnia, and acidosis, raising the risk of HbS polymerization and consequently, vaso-occlusive phenomena and other complications, such as transient ischaemic attacks and stroke. Frequencies of tonsillitis in SCD children with ATH (over five episodes in 12 months) is associated with increased painful crises.

Obstructive sleep apnoea (OSA)

In children with SCD, OSA is highly prevalent, ranging from 10% to 70% (h10). Children with SCA have a higher prevalence of sleep-disordered breathing consistent with OSA, beyond greater nocturnal desaturation, and experience typical nocturnal symptoms of snoring and breathing/sleep disturbances. However, the association between OSA and VOC frequencies, stroke or ACS has not been reported.

Factors related to SCD itself may be OSA promoters. Splenic infarctions, recurrent infections, or increased hematopoietic needs found in SCD leads to upper airway lymphoid tissue hypertrophy, causing ATH and consequently providing high risk OSA. Another proposed mechanism is that changes in the upper airway size of SCD patients occur as a result of bone marrow effects of the disease.

OSA risk factors in children include ATH, while OSA treatment in children with or without SCD involves tonsillectomy and/or adenoidectomy when episodes are recurrent. Continuous positive airway pressure can be a therapeutic option.

6. Psychosocial support and quality of life

6.1 Emotional support

Individuals living with SCD and their families may require support. Patients are at risk of anxiety and/or depression. The approach to care is all encompassing and includes timely and frequent psychological assessments.

The community should be mobilized to conduct health education on SCD, highlighting the need for emotional support for SCD patients. All patients with sickle-cell disease (children, adolescents, adults) should have a psychological assessment performed for the following: anxiety, depression, substance abuse, suicidal tendencies, experience of bullying, coping strategies, in addition to assessment of social engagement. Encourage patients and their families to join and/or create support groups.

6.2 Educational support

- SCD patients and their families should be provided with information on sickle-cell disease: general knowledge of sickle-cell disease, treatment and management of sickle-cell disease, knowledge on precipitating factors for crises and information on new research inclusive of new treatments and curative therapies.

- Educational resources can be provided by health care workers and with use of educational materials.
- There should be a common goal for both patients and providers to strengthen the school health programme to include SCD prevention and health promotion activities, and to provide education on the precipitating factors of sickle-cell disease.
- Patients should undergo comprehensive neuropsychological assessment for attention/ concentration deficits and cognitive deficits, as some patients will require special educational support.

6.3. Enhancing quality of life

The goal of care is to ensure that individuals with SCD remain in a steady state, lead a happy and fulfilled life, free from sickle-cell crises, debilitating complications and untimely death. Care of patients with SCD requires all levels of care with access to multidisciplinary teams of health care workers, trained in SCD specificities.

Educate to maintain a steady state of the SCD:

- Adhere to the routine prophylactic measures.
- Avoid added iron supplements unless prescribed.
- Ensure adequate and healthy diet.
- Educate on prevention of dehydration, acidosis, and other precipitating factors.
- Encourage routine health centre attendance at least once in three months during the steady state and especially when ill.
- Register at the antenatal clinic in the early phase of pregnancy or known or confirmed pregnancy.
- Join a support group for individuals with sickle-cell disease.
- Enrol confirmed cases into the health system and care teams.

The WHO Regional Office for Africa

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