NATIONAL GUIDELINES FOR CONTROL AND MANAGEMENT OF SICKLE CELL DISEASE IN KENYA

NATIONAL GUIDELINES FOR CONTROL AND MANAGEMENT OF SICKLE CELL DISEASE IN KENYA

First Edition

Ministry of Health

April 2020

MINISTRY OF HEALTH

National Guidelines for the Management of Sickle Cell Disease in Kenya

Published by:

Ministry of Health
P. O. Box 19982 KNH
Nairobi, 00202, Kenya
Email: ps@health.go.ke

Table of Contents

List of Figures

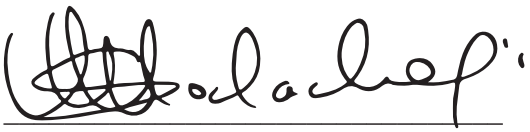
List of Tables

Acknowledgements

The development of Kenya's premier Sickle Cell Disease Control and Management Guidelines resulted from concerted efforts of various stakeholders, individuals and organizations in the Country. The Sickle Cell Technical Working Group under the leadership of Professor Fredrick Were wrote all the sections of this guidelines borrowing from best practices across the world and in line with current scientific evidence and experiences. We would like to thank all those who participated in the development of this vastly important endeavour. Of special mention are: The Ministry of Health in particular the National Blood Transfusion Services and Division of Non Communicable Diseases; Kenya Paediatric Association, Kenya Paediatric Research Consortium, the University of Nairobi, Moi University, Moi Teaching and Referral Hospital, Kenyatta National Hospital, Aga Khan University, Novartis, Toyota Tsusho and Laborex Kenya.

The Ministry further recognizes the diligent and tireless efforts of the Sickle Cell Technical Working Group from the writing to finalization of this document. It comprised staff from: Ministry of Health - Dr. Fridah Govedi, Dr. Jamlick Karumbi, Catherine Ahonge, Alex Kisyanga, Merine Owendi, Grace Wasike, Dr. Ephantus Maree; Kenya Paediatric Research Consortium-Professor Fredrick Were, Dr. David Githanga, Irene Amadi; the University of Nairobi/Kenyatta National Hospital-Professor Jessie Githanga, Dr. Fredrick Okinyi, Dr. Kibet Shikuku; Pharmacy and Poisons Board - Dr. Christabel Khaemba, Dr. Edward Abwao; Advocacy Groups-James Kago, Carlos Maube and Novartis - Dr. Tigist Gebre and Dr. Nathan Mulure.

The Manuscript does not allow us to mention all individuals and organizations who participated in this important exercise, therefore, to all of you not listed above we say, Asante Sana!



Susan Mochache, EGH
Principal Secretary
Ministry of Health

Executive Summary

The executive summary highlights key areas from the main text of the guidelines.

Introduction; Includes the global, regional and local epidemiological features of Sickle Cell Disease. It brings to light the interventions needed to control and manage this disease, laying emphasis on early diagnosis and the measures required to reduce the impact of complications and mortality. Overall improvement of quality of life is addressed. The rational for this guideline takes cognisant of the challenge's patients with sickle cell disease face and the complexities in provision of health care services thus calling for significant health system changes.

Background; This defines Sickle Cell Disease as an inherited blood disorder caused by the presence of abnormal haemoglobin (haemoglobin-HbS) in the red blood cells of affected individuals. This section gives a brief on the various forms of Sickle Cell Disease, risk factors, complications and burden estimated as almost 6,000 new-borns (one in every 150 new-borns) having had Sickle Cell in 2010 and this number would rise to over 10,000 (one in every 100 new-borns) per year by 2050 given the projected population growth. Disease pathophysiology, diagnosis and the wide spectrum of clinical presentation features are also discussed. These are heterogenous in nature and may be present in an acute or chronic form. The need for neonatal screening utilizing a testing algorithm has been emphasized for early identification and linkage to care and support systems. Key messages for Pre and Post Test Counselling are laid out and the immunization schedule to prevent infections that precipitate crisis in these patients.

Management; A clear and simplified systematic management approach to Sickle Cell Disease has been outlined beginning with the role of and appropriate use of Hydroxyurea as the key drug in prevention of Sickle Cell Disease crisis. Chronic transfusion therapy for management of this disease has been illustrated. Pain is the most frequent and distressing presentation for patients with Sickle Cell Disease, leading to frequent hospitalizations. Its management has been addressed here exhaustively to reduce suffering and long hospital stays. Preventive measures such as; malaria and penicillin prophylaxis, micronutrient supplementation, nutrition and immunization are elaborately covered the crucial role of psychosocial support for patients and their families is well addressed.

Management of Common Emergencies is exhaustively articulated. Reproductive health needs of patients with Sickle Cell Disease including pre-conceptual counselling, health promotion, haemoglobinopathy screening in the neonatal, premarital, antenatal and postnatal periods are included. The guidelines position Sickle Cell Disease care on a life course platform addressing patient needs at different stages from the newborn through to adulthood. Service delivery levels for Sickle Cell Disease have been defined and aligned to the Ministry of Health - Kenya Essential Package for Health levels. This Guidelines' document provides evidence-based recommendations for Sickle Cell Disease control and management in Kenya using patient-centred approach.

Dr. Patrick Amoth
Ag. Director General
Ministry of Health

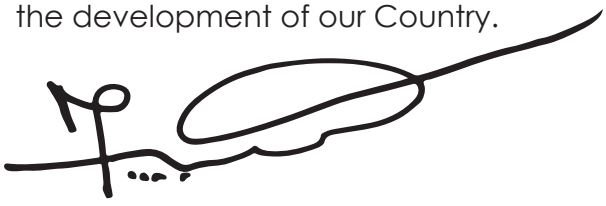
Foward

At least 240,000 children in Africa are born each year with Sickle Cell Disease of which an estimated 6,000 are in Kenya alone. In the absence of new-born screening and appropriate treatment, majority of such children die undiagnosed in early childhood from preventable causes such as malaria and bacterial infections. In Sub-Saharan Africa, an estimated 50-90% of those born with the condition die undiagnosed before their 5th birthday. The disease is common across Kenya with high disease burden pockets in Western, Nyanza and Coastal regions. Sickle Cell Disease is caused by a disorder in the haemoglobin component of blood leading to an abnormal sickle haemoglobin (Hb S). Individuals with sickle cell disease exhibit significant morbidity and mortality.

Today, I am greatly pleased to witness the end of this long journey of the development of Kenya's premier Sickle Cell Disease Control and Management Guidelines. The process has been a learning experience and was highly consultative based on up to date evidence based high impact intervention protocols from across the world. The Sickle Cell Technical Working Group had to work long hours embracing technology to develop these guidelines in spite the challenging period of the COVID-19 pandemic when evening curfew and social distancing was key to flattening the curve. These guidelines are aligned to the Health Sector Policy and Strategic direction, Vision 2030, the Constitution, Kenya Health Sector Strategic Plan and the Ministry's vision and mission which recognize Kenyans right to the highest standard of health. Key areas covered in these guidelines are presented in a simplified manner using a public health approach to Sickle Cell Disease Control and Management. As Kenya rolls out one of its 'Big Four Agenda' on Universal Health Coverage and Sickle Cell Disease transitions from a condition that is fatal in early life to a chronic condition needing life-long care hence requiring preparedness of our health services. These guidelines are just what we need.

The guidelines propose delineation of unique levels of service delivery for patients with Sickle Cell Disease aligned with the Kenya Essential Package for Health levels. These guidelines articulate the requisite guidance for standardized management of Sickle Cell Disease at all levels from diagnosis, management and appropriate referral. The suggested levels I to IV involving all facilities in Kenya emphasize the national commitment to this course and make sicklers safe anywhere in Kenya. The suggested cascade of care is indeed innovative.

I, therefore, urge all healthcare personnel regardless of sector to use these guidelines for early diagnosis, intervention and effective management of patients with Sickle Cell Disease for better outcomes with the aim of ensuring these patients enjoy quality life and contribute to the development of our Country.



Hon. Mutahi Kagwe, CBS
Cabinet Secretary
Ministry of Health

Abbreviations

Ab Antibody
ACE Angiotensin Converting Enzyme
ACS Acute Chest Syndrome
ADR Adverse Drug Reaction
ANC Acute Neutrophil Count
AST Aspartate Amino-Transferase
AVN Avascular Necrosis
BP Blood Pressure
CAM Cellulose Acetate Membrane
CBC Complete Blood Count
CKD-EPI Chronic Kidney Disease Epidemiology
CNS Central Nervous system
CRP C Reactive Protein
CT Computed Tomography
CVA Cerebral Vascular Accident
CVP Central Venous Pressure
CXR Chest X-ray
DOB Date of Birth
EEG Electro Encephalogram
ENT Ear Nose and Throat
ESR Erythrocyte Sedimentation Rate
G6PD Glucose 6-Phosphate Dehydrogenase
GCS Glasgow Coma Scale
GFR Glomerular Filtration Rate
HB Hemoglobin
HCV Hepatitis C Virus
HE Hemoglobin Electrophoresis
HIV Human Immunodeficiency Virus
HPLC High-Performance Liquid Chromatography
HR Heart Rate
ICP Intra-Cranial Pressure
ICU Intensive Care Unit
IEF Isoelectric Focusing
IV Intravenous
LDH Lactate Dehydrogenase
LFT Liver Function Test
LP Lumbar Puncture
MCV Mean Corpuscular Volume
MRA Magnetic Resonance Angiography
MRI Magnetic Resonance Imaging
NBTS National Blood Transfusion Service
NG Naso Gastric
OFC Occipitofrontal Circumference
PCR Polymerase Chain Reaction
PCV Pneumococcal Conjugate Vaccine
PH Pulmonary Hypertension
PPSV Pneumococcal Polysaccharide Vaccine
PRN Pro-RE Nata (When Necessary)
RBC Red Blood Cells
ROM Range of Movement
SaO2 Oxygen saturation
SCA Sickle Cell Anaemia
SCD Sickle Cell Disease
SCN Sickle Cell Nephropathy
TBV Total Blood Volume
TCD Trans Cranial Doppler
TENS Transcutaneous Electrical Nerve Stimulation
URTI Upper Respiratory Tract Infection
UTI Urinary Tract Infection
VOC Vaso Occlusive Complications
WBC White Blood Cells

Acronyms

BABY-HUG Paediatric Hydroxyurea Trial
REACH Realizing Effectiveness Across Continents with Hydroxyurea

Introduction

Globally, it is estimated that Sickle Cell Disease (SCD) causes between 6-15% deaths in children aged less than 5 years[1]. There is paucity of data in Kenya, but in general, malaria endemic areas have a higher prevalence of SCD. Interventions to control the disease include provision of prompt and effective management, advocacy, communication and social mobilization for screening, genetic counselling during premarital courtship. A child born with sickle cell disease is ten times likely to die than a normal child. Morbidity and mortality have been high in young children with sickle cell disease. However, recent studies have shown that early diagnosis and supportive care have significant impact in the reduction of complications, mortality and improved quality of life. The emphasis must now move towards early detection and prevention of long-term complications of sickle cell disease[2]. This early diagnosis of Sickle Cell Disease is important to initiate prompt management.

Management of SCD has become increasingly multi-disciplinary and complex. This calls for the development of guidelines for the management of specific clinical problems and protocols for various therapeutic procedures; to facilitate uniformity and standardization of care across different disciplines. Such guidelines and protocols should be regularly revised and updated in line with developments in clinical practice and findings from scientific research. Given the current scarcity of local data, it is useful to take advantage of existing platforms like the Kenya Health Information System (formerly DHIS2) together with periodic surveys to help future updates. The research and academic community in Kenya will have to take leadership in this.

Rationale

Persons living with Sickle Cell Disease are faced with numerous health challenges. Their health care provision is increasingly becoming complex and requires a multidisciplinary approach. With improved care, the burden of Sickle Cell Anaemia is set to reduce. Kenya currently does not have standardized guidelines for the management of SCD and thus the development of these comprehensive recommendations for the early detection and management of the condition. Such guidelines should be evidence-based and regularly revised and updated as new research emerges. Provision of guidelines will allow for policy decisions and strategies in the management of SCD.

Objective

The objective of these guidelines is to provide the target audience with evidence-based recommendations for the management of SCD. Guidelines are given for the early diagnosis, prevention and management of symptoms and complications of SCD, including in special risk groups such as pregnant women and those scheduled for surgery.

Target audience

These guidelines are intended for all health professionals, public health and policy specialists, research institutions and health professionals training institutions. Non-governmental organizations and agencies working as partners in health or SCD control may also find this guideline useful.

[1]Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ 2008; 86: 480–87.
[2]Uyoga S, Macharia AW, Mochamah G, Ndila CM, Nyutu G, Makale J, et al. The epidemiology of sickle cell disease in children recruited in infancy in Kilifi, Kenya: a prospective cohort study. Lancet Glob Heal 2019;7:e1458–66. doi:10.1016/S2214-109X(19)30328-6.

Background

Definition

Sickle Cell Disease (SCD) is an inherited blood disorder caused by presence of abnormal haemoglobin (haemoglobin-HbS) in the red blood cells of affected individuals. It is the most common severe monogenic disorder in humans and is characterized by presence of sickle shaped red blood cells in the blood. This sickle shaped red blood cells have a markedly reduced life span of about 16 days compared to 120 days for normal red blood cells. The cells are sticky and have difficulty passing through small blood vessels causing blockage of the blood flow leading to damage of tissues and organs, ultimately causing many of the manifestations of the disease[3].

Forms of Sickle Cell Disease

Several forms of Sickle Cell Disease exist with the most common being haemoglobin SS (HbSS) disease, due to homozygous state for HbS. Other forms result from co-inheritance of HbS and another haemoglobinopathy (heterozygous forms) such as sickle-hemoglobin C disease (HbSC) and sickle beta-plus-thalassemia (HbSβ+) sickle-beta-zero-thalassemia (HbSβ0). HbSS and HbSβ0-thalassemia are clinically very similar and therefore are commonly referred to as sickle cell anaemia.

The Sickle Cell Trait (SCT), Hb AS, (or carrier) is not categorized as a form of disease and individuals have a normal life expectancy. However, under certain situations such as high altitudes and extreme physiological stress, they may suffer from complications. Individuals with SCT are more likely than normal individuals to suffer from kidney abnormalities. SCT carriers should be identified and provided with education and genetic counseling.

Risk factors of Sickle Cell Disease complications

Children under 5 years of age are at increased risk of death from infections, anaemia and other life-threatening complications of SCA, many of which can be prevented through effective and inexpensive prophylaxis (e.g. prophylactic administration of penicillin, pneumococcal immunizations, distribution of malaria bed nets) and education of parents about the importance of seeking medical attention for fever and other preventive measures for SCD complications if diagnosed early in life. Some of the triggers for sickling in SCA include dehydration, cold, infection, hypoxia, fever, severe physiologic or emotional stress.

Disease Burden

Sickle Cell Disease affects 20-25 million of people globally, of which 12-15 million live in Africa. The natural distribution covers a broad belt, including the Mediterranean, western, parts of East and Central Africa, the Middle East, India and South East Asia. It is estimated that 75-85% are children born in Africa where 50-80% of children born with the disease die before the age of 5 years. In Sub-Saharan Africa, approximately 240,000 children are born with Sickle Cell[4] . There is paucity of population level data but in general, based on model projections it is estimated that almost 6,000 newborns (one in every 150 newborns) had Sickle Cell in 2010 and this number could rise to over 10,000 (one in every 100 newborns) per year by 2050[5]. The distribution reflects the fact that Sickle Cell Trait confers a survival advantage against malaria and that selection pressure due to malaria has resulted in high frequencies of the mutant gene especially high malarial transmission areas.

[3]Amendah DD, Mukamah G, Komba A, Ndila C, Williams TN. Routine Paediatric Sickle Cell Disease (SCD) Outpatient Care in a Rural Kenyan Hospital: Utilization and Costs. PLoS One 2013;8:1–6. doi:10.1371/journal.pone.0061130.

[4]Mulumba LL, Wilson L. Sickle cell disease among children in Africa: An integrative literature review and global recommendations. Int J Africa Nurs Sci 2015; 3:56–64. doi: 10.1016/j.ijans.2015.08.002.

[5]Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN (2013) Global Burden of Sickle Cell Anaemia in Children under Five, 2010–2050: Modelling Based on Demographics, Excess Mortality, and Interventions. PLoS Med 10(7): e1001484. https://doi.org/10.1371/journal.pmed.1001484

Inheritance of the mutation at both alleles (HbSS) predisposes individuals to severe malaria with increased mortality. It also increases mortality from other complications of SCD[6]. In Kenya, the prevalence varies in regions and mimics the malaria endemicity. In the western region it is estimated that as high as 18% of children are born with a Sickle Cell Trait and 4.5% will end up developing SCD[7]. In the lake region, it is estimated that about 17% children are carriers of the trait with 0.6% having SCD[8] while in the coastal region, using inpatient data, almost 1% of inpatient children have SCD and are almost 20 times likely to die compared to admissions of other morbidities[9]. Movement in search of better livelihoods leads to a wider spread of the areas previously considered endemic zones.

The high mortality rates are influenced by multiple factors including limited resources leading to poor access to care and lack of comprehensive SCD management programs.
Interventions that have been effective in reducing mortality among SCD patients in high resource settings such as newborn screening, and prophylactic penicillin administration are not available in most low resource countries.

Diagnosis

Diagnosis of SCD is based on clinical presentation, personal and family history, clinical features (signs/symptoms) and laboratory testing.
In this section, we describe the clinical presentation that a clinician should be able to pick and suspect SCD especially during the first contact with a health care facility. The importance of drawing the family pedigree through thorough history taking so as to ascertain the family history for the condition is emphasized (Figure 4)

Clinical features

The spectrum of clinical expression is heterogeneous with some people having mild disease while others present with complications. These include:

Acute presentation

i. Vaso-occlusive crisis especially painful crisis: dactylitis (painful swelling of hands and feet) , severe back pain, pain localized to specific limbs (upper or lower limbs), chest pain or abdominal pain
ii. Other vaso-occlusive crises such as acute chest syndrome (fever with new onset shortness of breath), stroke (manifest as weakness of limbs depending on region affected or other neurological sequalae), priapism
iii. Haemolytic crisis: symptomatic anemia presenting as fatigue/extreme tiredness or decreased activity or irritability with increasing jaundice (yellowness of eyes, palms and soles of feet in pediatric population)
iv. Aplastic crisis: symptomatic anemia as described above usually resulting from parvovirus B19
v. Sequestration crisis: notable increase in spleen or liver size more so in paediatric age group. This can result in symptomatic anemia with or without hemodynamic instability

NB: the above may be associated with infective process presenting with fever.

[6]WHO. Sickle-cell anaemia Report by the Secretariat. 2006.
[7]Christopher M. Wanjiku, Festus Njuguna, F. Chite Asirwa, Samuel Mbunya, Cyrus Githinji, Christopher Roberson, Anne Greist; Establishing care for sickle cell disease in western Kenya: achievements and challenges. Blood Adv 2019; 3 (Supplement 1): 8–10. doi:
[8]Otieno W, Estambale B, Aluoch JR, et al. Association between Sickle Cell Trait and Low Density Parasitaemia in a P. falciparum Malaria Holoendemic Region of Western Kenya. IJTDH. 2012;2:231–40
[9]Uyoga S, Macharia AW, Mochamah G, Ndila CM, Nyutu G, Makale J, et al. The epidemiology of sickle cell disease in children recruited in infancy in Kilifi, Kenya: a prospective cohort study. Lancet Glob Heal 2019;7:e1458–66. doi:10.1016/S2214-109X(19)30328-6.

Chronic presentation:

i. Gallstones sometimes predisposing to acute cholecystitis
ii. Chronic leg ulcers
iii. Avascular necrosis of the head of the femur causing limping with shortened limb
iv. Target organ disease e.g. renal dysfunction, cardiac etc.

Laboratory Diagnosis

The laboratory diagnosis of sickle cell disease can be considered as neonatal screening and diagnosis after the neonatal period as discussed below:

Neonatal Screening

To determine the Hb type through separation techniques on extracted material from dried blood spots. Initial newborn screening test results should be confirmed by follow-up studies with a different method for Hb separation (see Figure 1: Neonatal Screening Algorithm). Tests used for newborn screening include Isoelectric Focusing (IEF), High Performance Liquid Chromatography (HPLC) or Haemoglobin Electrophoresis described in more details below.

Diagnosis after the Neonatal Period

This is through careful assessment of the clinical features, complete blood count, reticulocyte count, peripheral blood morphology and Hb separation techniques, family studies and if necessary, genetic testing. This diagnosis is categorized into preliminary tests and confirmatory tests. (See Figure 2: Post Neonatal Period Screening) for the diagnosis algorithm.

1. Preliminary Tests

a. Full blood counts, reticulocyte counts, blood film morphology

In the blood counts the main features are a reduction in the Hb (anaemia) that could be normocytic or macrocytic (with increased hemolysis or for patients on Hydroxyurea). Microcytic red blood cells may occur in SCD if it co- exists with beta thalassemia, or iron deficiency. The reticulocyte count is raised due to hemolysis that occurs with the disease. On peripheral smear, irreversibly sickled RBCs may be seen, polychromasia and presence of nucleated red blood cells which are in keeping with the hemolytic process. RBC inclusions -Howell Jolly bodies - that may indicate splenic dysfunction may be seen.

b. Sickling Test

This test can be easily performed in a laboratory at lower level facilities. The test will be positive in individuals with Sickle Cell Disease as well as in Sickle Cell Trait. Hb separation technique is necessary once it is positive as it does not distinguish the different forms of SCD. This test should, however, NOT be used for screening newborns and is not advisable for children as it may give false negative results due to elevated HbF levels. The test is also of no added value if the blood film morphology shows Sickle Cells.

c. Haemoglobin Solubility Test

This method detects the presence of HbS and will be positive in individuals with homozygous forms (HBSS) heterozygous forms (HbSC, HbSβ-thalassaemia) and in SCT. False negative tests may occur due to high levels of foetal haemoglobin (i.e. low concentrations of Hb S) in infants with SCD. This test can be performed in the lower level laboratories. An Hb separation technique is necessary once it is positive as it does not distinguish the different forms of SCD. The test is of no added value if the blood film morphology shows sickle cells.

2. Confirmatory Tests

a. Haemoglobin Electrophoresis (HE)

This is one of the Hb separation methods and here the determination of the type of Hb depends on the migration of the different forms through a medium that conducts electricity when subjected to an electrical field. The final position of a haemoglobin type depends on the pH of the medium and the charge of the haemoglobin molecule. Capillary HE allows for differentiation as well as quantification of the different types of haemoglobin. This test can be performed at level 4 facilities and above.

b. High-Performance Liquid Chromatography (HPLC)

HPLC allows for quantification of normal and variant haemoglobins even at low concentrations, enabling differentiation of Hb Sβ0 and Hb Sβ + thalassaemia from HBSS as well as identification of compound heterozygous disorders such as Hb S-HPFH (hereditary persistence of fetal hemoglobin). It may be used for neonatal screening. This test can be performed at level 4 facilities and above.

c. Isoelectric Focusing (IEF)

This is a type of electrophoresis that is used for separation of different types of haemoglobin. It is often used for neonatal diagnosis.

3. Point of care rapid tests

Several rapid point of care tests are available in the market and have been shown to have high specificity and sensitivity when compared to the HPLC[10]. These are useful at the lower level facilities where more conventional Hb separation techniques are unavailable and rapid results are needed. These tests will identify Hb A, Hb S, Hb C. However, they cannot quantify the different haemoglobins or identify accurately other forms of SCD such as Hb S β-thalassaemia. Confirmation of the results can be done using Hb electrophoresis, HPLC or IEF. These tests are useful in the identification of SCT/ carriers.

4. Other ancillary laboratory investigations useful in detection and monitoring of the disease include:

a. Biochemical changes include elevated levels of Lactate Dehydrogenase (LDH), low haptoglobin, high total indirect bilirubin and mildly high aspartate aminotransferase (AST).

b. DNA analysis using Polymerase Chain Reaction (PCR) are used for prenatal, preimplantation diagnosis or in situation where haemoglobinopathy cannot be confirmed by the special hematological tests.

[10]Segbena AY, Guindo A, Buono R, Kueviakoe I, Diallo DA, Guernec G, et al. Diagnostic accuracy in field conditions of the sickle SCAN® rapid test for sickle cell disease among children and adults in two West African settings: The DREPATEST study. BMC Hematol 2018;18:1–10. doi:10.1186/s12878-018-0120-5. Kutlar F. Diagnostic approach to hemoglobinopathies. Hemoglobin. 2007;31(2):243-50.

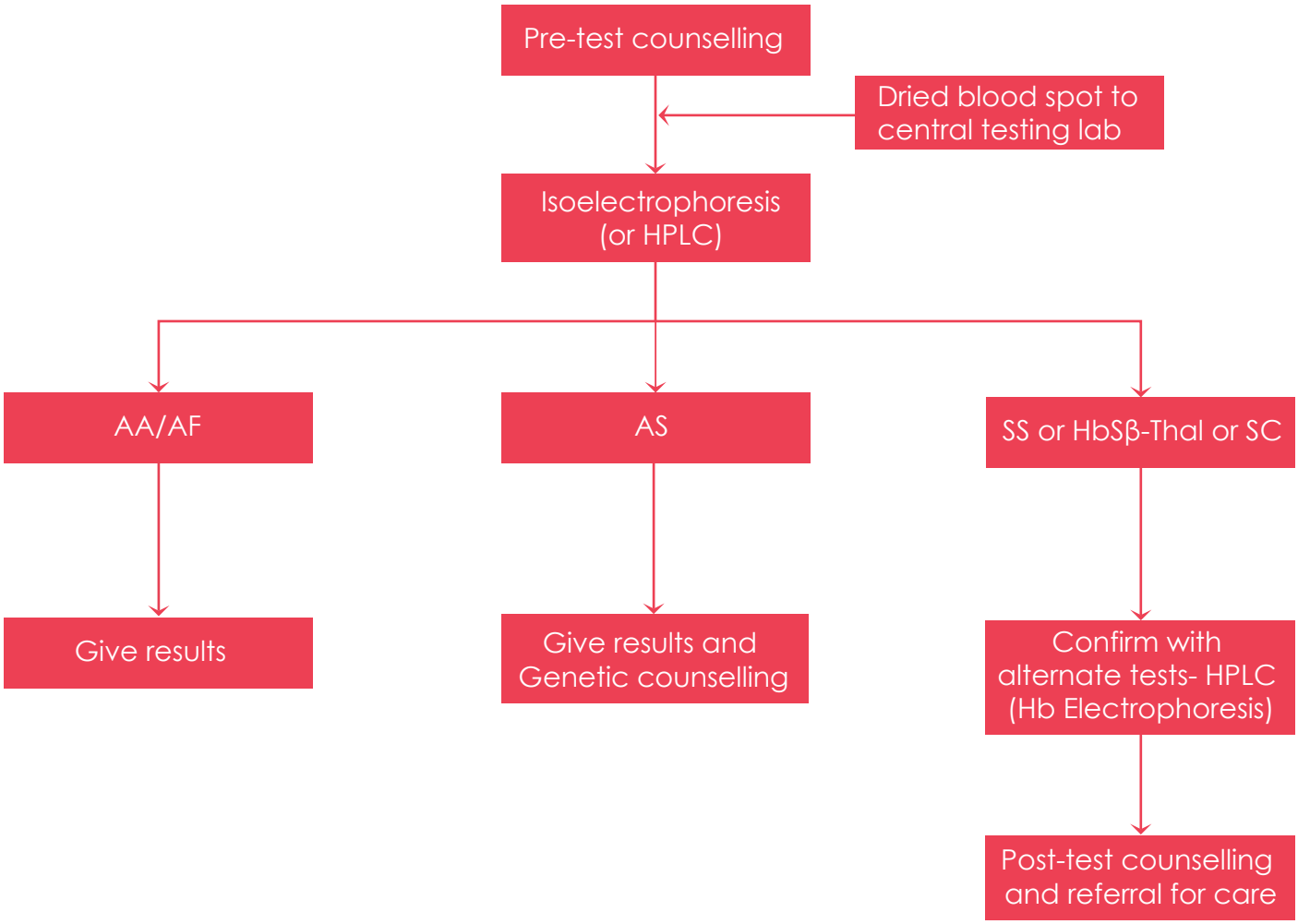


Figure 1: Pre neonatal period alogarithm

[10]Segbena AY, Guindo A, Buono R, Kueviakoe I, Diallo DA, Guernec G, et al. Diagnostic accuracy in field conditions of the sickle SCAN® rapid test for sickle cell disease among children and adults in two West African settings: The DREPATEST study. BMC Hematol 2018;18:1–10. doi:10.1186/s12878-018-0120-5. Kutlar F. Diagnostic approach to hemoglobinopathies. Hemoglobin. 2007;31(2):243-50.

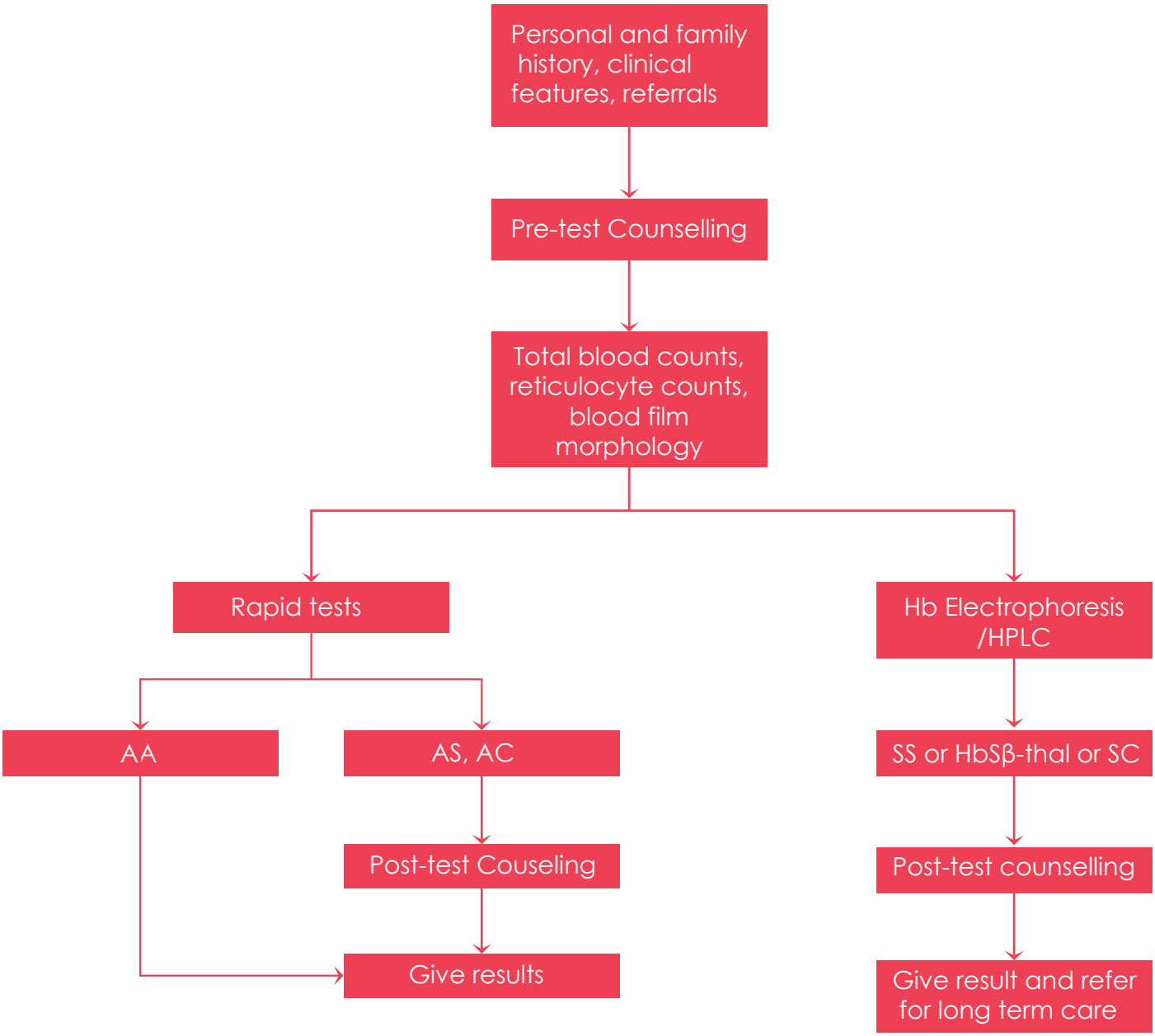


Figure 2: Post neonatal period screening

Management of Sickle Cell Disease

Management of patients with SCD requires a multidisciplinary approach in order to cater for acute and chronic complications of the disease. Comprehensive management of SCD is a group of evidence-based interventions that are geared towards reduction of morbidity and mortality from the disease and improve quality of care of these patients and their families.

Comprehensive care of SCD begins with appropriate diagnosis preferably during the newborn period; the start of penicillin prophylaxis started before the age of 2 months and continued upto 5 years; immunization practices; safe transfusion practices; psychosocial support for the patient and families; nutritional support with folic acid supplementation; appropriate pain management; routine follow up clinics; hydroxyurea use and screening for chronic complications of SCD.

Newborn Screening for SCD

The best approach is to have nationwide screening of all newborns for SCD but this comes with challenges of limited resources. Inclusion of children born at home has a financial implication to the health budget. A targeted approach where all newborns in high endemic areas are tested shortly after birth and early screening and testing of suspected children in potentially low endemic areas may be used as an alternative. The Cooperative Study of Sickle Cell Disease study (CSSD) identified that most of the children with sickle cell disease died before their second birthday due to infection and anemia hence the need to identify these patients even before they shown signs of disease.

Penicillin Prophylaxis

Patients with SCD are prone to infection and death from encapsulated bacterial organisms like *Streptococcal pneumoniae* due to splenic dysfunction that occurs within the first 5 years of life. It is therefore recommended that children with SCD should have penicillin prophylaxis started within 2 months of life and continued until 5 years of age. However, for patients who have had surgical splenectomy, it is given for life. Its use may be continued until later in life for children who have had more than two episodes of severe pneumonia. The dose of Pe***nicillin V is as follows:***

- ***Children less than 3 years: Penicillin V syrup 125mg twice daily***
- ***Children more than 3 years: Penicillin V syrup/tablets 250mg twice daily***
- ***Patients with penicillin hypersensitivity may use erythromycin as an alternative***

Immunization Practices

Children with SCD are should get all the vaccines as per the Kenya Expanded Programme on Immunization which covers infectious diseases that are relevant to SCD like Streptococcal pneumonia, Hemophilus influenza type B and Hepatitis B. It is however recommended that they get additional vaccines and boosters as follows:

Table 1: Vaccine Schedule

Vaccine	Schedule
Pneumococcal Polysaccharide Vaccine (Pneumo-23)	At 2 years and once every 5years
Influenza vaccine	Annually
Meningococcal vaccine	2 doses for those below 2 years of age and one dose for those above 2years
Hemophilus influenza type B	Booster at 18months

Hydroxyurea Use

The CSSD study was a landmark prospective cohort study that demonstrated the benefits conferred by use of hydroxyurea in SCD like reducing painful crisis, blood transfusion and infection in patients with SCD. The Ped- HUG and Baby- HUG trials have also demonstrated the benefits of hydroxyurea use in children with no safety concerns. The REACH trial in which Kenya was one of the four participant countries, also confirmed the clinical benefits hydroxyurea in children with sickle cell disease and co-morbidities like malaria and malnutrition and also did not show any safety concerns in these patients.

The table below summarizes indications for starting hydroxyurea and baseline laboratory test:

Table 2: Starting hydroxyurea and baseline laboratory test

Indications	Baseline laboratory monitoring
1.Child over 9 months with SCD 2. Adult with 3 or more severe VOCs during any year. 3. Severe and/or recurrent ACS (2 or more episodes in a lifetime) 4.Chronic anaemia interfering with daily activities or quality of life 4.When chronic transfusion therapy is not feasible for preventing new or recurrent stroke. 5.Recurrent priapism 6.Chronic kidney disease and are taking erythropoietin	1.Full Blood Count 2.Reticulocyte count 3.Quantification of HbF (% HbF) 4.Serum electrolytes, urea, and creatinine 5.Liver function tests 6.Urine Pregnancy Test in women

Laboratory monitoring of patients on hydroxyurea requires a full blood count done every 8-12 weeks and liver functions tests done every 12 weeks initially until when on a stable dose and thereafter when necessary.

The approaches of Hydroxyurea dosage include:

a. Standard dosing
In this approach a fixed dose is selected within the recommended range and used for patients without escalation for example a dose of 20 mg/Kg/day (unless dose limiting toxicity is experienced).

b. Escalating dose to maximum tolerable dose
In this approach, patients are started on the lower therapeutic range and the dose increased every 8-12 weeks until the dose limiting toxicity (myelosuppression or hepatotoxicity) is experienced or until a maximum of 35mg/kg/day is reached.

c.Hydroxyurea is available mainly as capsules which have limitations when used in children with challenges in dosing and administration occur. Liquid formulations (syrup) can be prepared and have a shelf life of between 14-90 days thus making hydroxyurea use in pediatrics practical.

The figure below illustrates an algorithm to guide hydroxyurea use.

Hydroxyurea Therapy

Starting dosage
Adults: 15mg/kg/day (5-10 CKD)
Children: 20mg/kg/day

→ **FBC monitored monthly** for the first 2-3 months. ANC>2 x 10^9/l Hb level >4.5 g/dl platelet count >80 x 10^9/l

Poor clinical response

Increase dose by 2.5 to 5mg/kg/day Give for 1-3 months FBC monitored monthly for the first 2-3 months. ANC>2 x 10^9/l, Hb level >4.5 g/dl, platelet count >80 x 10^9

Poor clinical response

Increase dose by 2.5 to 5mg/kg/day Give for 1-3 months FBC monitored monthly for the first 2-3 months. ANC>2 x 10^9/l, Hb level >4.5 g/dl, platelet count >80 x 10^9

Poor clinical response

Continue increasing the dose in this step-wise gradual manner till a clinical response is achieved ensuring that the FBC monitored monthly for the first 2-3 months and ANC>2 x 10^9/1 max, Hb level >4.5 g/dl, platelet count >80 x 10^9 (ceiling dose) 35mg/kg/day

Good clinical response

Good clinical response

Continue at fixed dose FBC monitored every 2-3 months if counts remain stable

Good clinical response

Continue at fixed dose FBC, retic monitored every 2-3 months if counts remain stable

Key
ANC - Absolute neutrophil count
HB - Haemoglobin
CKD - Chronic kidney disease
FBC - Full blood count
Retic - Reticulocyte count

Contraindications

Hydroxyurea should be discontinued
1. All pregnant women
2. All breast-feeding women
3. At least three months prior to conception in both males and females.

Side effects

1. Myelotoxicity
2. Mouth ulceration
3. Macrocytosis & megaloblastic changes
4. Nausea
5. Skin toxicity rashes & hyperpigmentation

Reporting adverse reactions

Reporting suspected adverse reactions allows continued monitoring of the benefit/risk balance of the products. Healthcare professionals are asked to report any suspected adverse reactions via the **Yellow Form** at: **www.pv.pharmacyboardkenya.org** or download the form at **https://pharmacyboardkenya.org/pharmacovigilance.**

Any patient that develops life threatening Adverse Drug Reactions should be issued with a Patient Alert Card for presentation during subsequent visits

Figure 3: Hydroxyurea therapy and side effects

Refs:
Inusa B, Atoyebi W, Hassan A, et al Low-dose hydrozycarbamide therapy may offer similar benefits as maximum tolerated dose for children and young adults with sickle cell disease in low-middle income settings. F1000Research 2018, 7(F1000 Faculty Rev):1407 Last updated: 27 SEP 2018
Thornsburg CD, BA, Luo Z, Miller ST, et al. Impact of hydroxyurea on clinical events in the BABY HUG trial. Blood 2012 Nov 22;120(22): 4304-4310.

Blood Transfusion in SCD

Blood transfusion is a key therapeutic modality in SCD. All staff involved in the prescription and administration of blood and blood products must be familiar with the NBTS transfusion guideline. Blood transfusion in the emergency will serves to increase the oxygen-carrying capacity and to reduce vaso-occlusive complications.

Blood transfusion may be through a simple (top-up) transfusion or exchange transfusion. Exchange transfusion is used to reduce the concentration of HbS in circulation (usually to <30%) without increasing the haematorit or whole blood viscosity. This is required in some complications of the disease such as treatment of acute ischemic stroke, acute chest syndrome (ACS), priapism or peri-operatively. Exchange transfusion may be performed using the manual method or by using apheresis equipment.

Table 3: Indications for emergency transfusion

Condition	Comment
Acute anaemia (drop in Hb >2g/dl from normal steady state Anemia <5g/dl Symptomatic anemia	Simple transfusion
Acute ischaemic sequestration	Simple transfusion
Acute ischaemic stroke	Exchange transfusion to Hb of 10g/dL, HbS <30%
Acute chest syndrome	Depending on severity: No transfusion, simple or exchange transfusion
Acute priapism	Consider simple or exchange transfusion if no response to initial treatment
Multiorgan failure, acute sickle hepatopathy, severe sepsis	Exchange transfusion to Hb 10g/dL, HbS <30%

Chronic Transfusion Therapy

The aim of chronic transfusion therapy is to keep the HbS level <30% (depending on the clinical situation). This can be achieved by regular top up transfusions keeping the Hb between 10 - 11g/dl, typically every 3 - 6 weeks. Note that iron overload must be prevented/ managed. See annex 2 Iron chelators to be considered during transfusion. This can be measured using HPLC and Hb Iso-electrophoresis.

Table 4: Indications for chronic transfusion therapy

Condition	Comment
Primary stroke prevention	Simple regular transfusions (every 3-4 weeks) to maintain Hb at 10g/dL
Prevention of stroke recurrence	Simple regular transfusions (every 3-4 weeks) to maintain Hb at 10g/dL
Recurrent acute chest syndrome	Consider if other treatments (e.g. hydroxyurea) not effective or contraindicated. Simple transfusion
Chronic organ damage such as chronic renal failure or chronic lung disease	Simple regular transfusions (every 3-4 weeks) to maintain Hb at 10g/dL
Intractable or very frequent painful crisis	Consider if other treatments (e.g. hydroxyurea) not effective or contraindicated.
Pulmonary hypertension	Consider on case by case basis
Leg ulcers	Consider if other treatments (e.g. hydroxyurea) not effective or contraindicated.

Types of Blood Products

Simple transfusion:

- Packed red cells are preferred for simple transfusion. The haematocrit of the donor blood should be about 0.6. (60%)
- The formula below shows how to estimate the blood volume to be transfused. Care must be taken to avoid hypervolemia which can give rise to further complications. Where a relatively large volume of blood is to be administered one must check the HB and Haematocrit after transfusing some of the blood to avoid over transfusing.

Table 5: Formulae for estimating the volume of PRC in a paediatric and Adult Patients

Child	Adult
PRBC vol = $\frac{\text{Weight (kg) x Hb increment (g/dL) x 3}}{0.6}$ 10 mL/kg gives an increment of 2 g/dL	One unit of whole blood/PRBC can increase Hb by 1g/dL or Hct by 3%

Exchange transfusion;
This should be done by individuals with requisite knowledge, skills and practical experience. Details are beyond the scope of these guidelines

Pain Management in SCD

One of the hallmarks of SCD is vaso-occlusive crisis for which pain is the most distressing symptom for most patients and their families. Each institution, requires to adopt pain assessment tools and administer pain medications as early as possible as recommended by the World Health Organization ladder, round the clock, and by the patient. Below are some pain assessment tools that can be used depending on the patient's age and other characteristics.

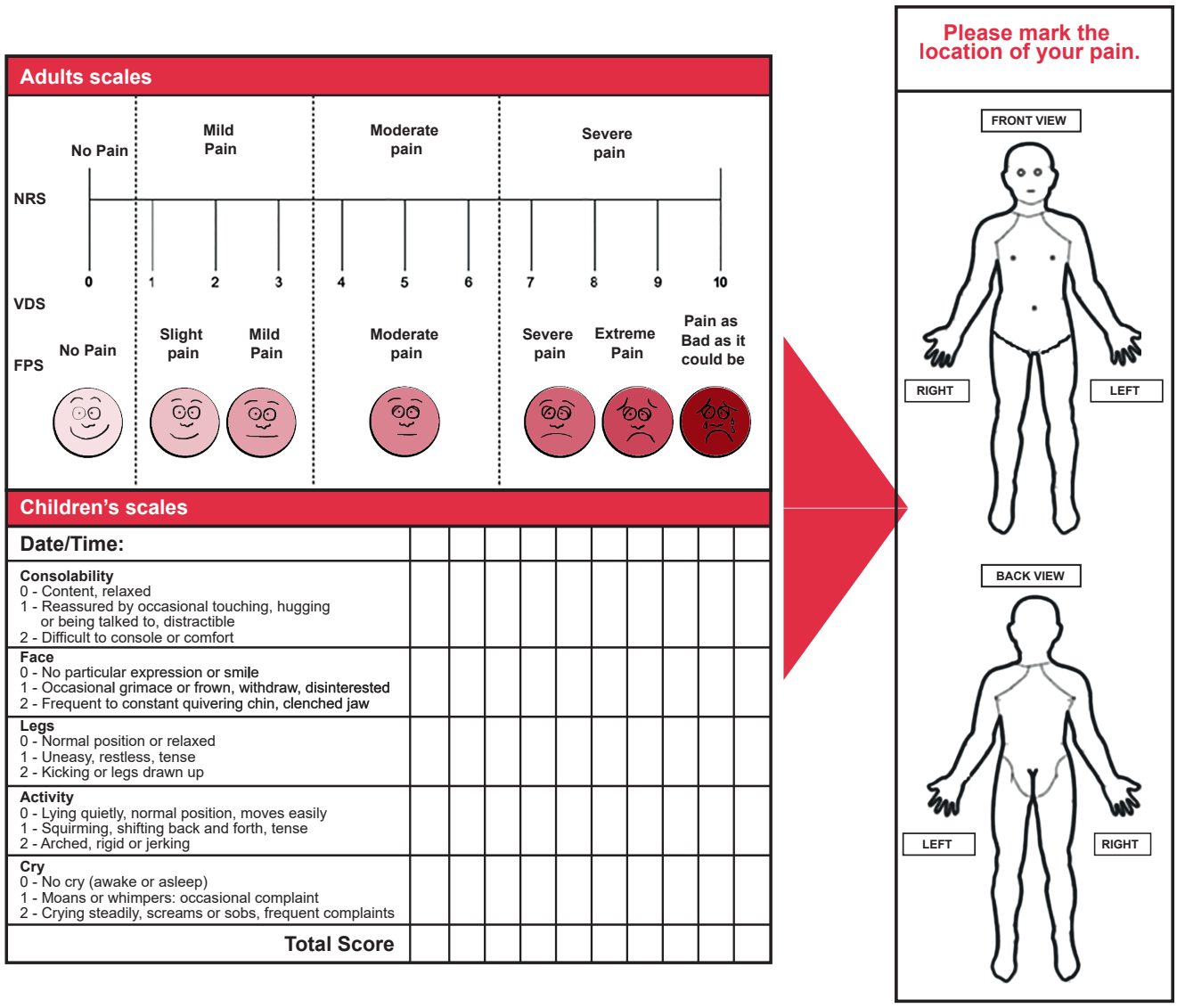


Figure 3: Assessment and classification of pain

Parents can be taught how to use analgesics like paracetamol and Non- steroidal anti-inflammatory drugs (NSAIDS) and other non-pharmacological methods at home. However, for patients in the hospital, pain needs to be assessed as the fifth vital sign and managed appropriately. The fear of addiction that health care workers have when using opioids in children with SCD has been shown to be unreal and uncontrolled pain found to have negative effects on patients.

The availability of opioids like morphine requires to be addressed in order to manage SCD pain appropriately. Several formulations like intravenous/ patches/oral forms (in tablets/ syrup) need to be availed.

Table 6: Pain Management Based On Severity

PAIN AND APPROPRIATE MEDICAL MANAGEMENT		
MILD	**MODERATE**	**SEVERE**
Reassurance, hot packs, reposition, massage, distraction **Child: paracetamol 15mg/kg qds** **Adult: paracetamol 1g qds**	Treat as Mild pain and ADD Child: Ibuprofen 5mg/kg TDS OR Diclofenac 1mg/kg TDS Adult: Ibuprofen 400mg TDS OR Diclofenac 100mg TDS	Treat as Moderate and ADD Child: Oral morphine** 0.5mg/kg 3-4 hourly as needed Adult: Oral morphine 5-10mg 3-4 hourly as needed

Table 7: Drugs Used In Pain Management

Drug	Single dose for child >1month	Freq.	Forms available	Comment
Paracetamol[b] (Available in Oral and IV formulations)	10–15mg/kg PO OR by age; 3–12mth: 60mg – 120mg 1– 5yrs: 120mg – 250mg 6–12yrs: 250mg – 500mg >12yr: 500mg – 1g	4– 6hrly	Tablets 500mg Liquid 120mg/5ml 250mg/5ml	Maximum[d]: 60mg/kg/day OR 4g/day whichever is lower
	IV Formulation ≤10 kg[c] -7.5mg/kg > 10 kg to ≤33kg -15mg/kg > 33 kg to ≤50kg - 15mg/kg >50kg with additional risk factors for hepatotoxicity – 1gm >50kg with no additional risk factors for hepatotoxicity – 1gm	4– 6hrly	125mg/ml solution 10mg/ml solution	Maximum[d]: 30mg/kg/day 60mg/kg not exceeding 2g 60mg/kg not exceeding 3g
Ibuprofen[b]	5mg/kg PO OR 1– 2yrs: 50mg PO 3– 7yrs: 100mg PO 8–12yrs: 200mg PO >12yrs: 200 – 600mg PO	6– 8hrly	Tablets 200/400/600mg AND 800mg retard Soluble Tabs 200mg Liquid 100mg/5ml Granules 600mg pack	Maximum: 2.4g daily

[b] For patients who are on NSAID to check on the hepatoxicity, GIT, Cardiac renal complications.
[c] Pre-term newborn infants: No safety and efficacy data are available for pre-term newborn infants on paracetamol IV use
[d] The maximum daily dose as presented in the table above is for patients that are not receiving other paracetamol containing products and should be adjusted accordingly taking such products into account

Table 7: Drugs Used In Pain Management

Diclofenac[b] (available in IV & Rectal formulations)	300mcgs – 1mg/kg PO/PR Diclofenac Suppositories **Adults** initial daily dose is 100 to 150 mg. In milder cases, as well as for long-term therapy, 75 to 100 mg daily **Pediatric patients** 1 -14years 0.5 to 2 mg/kg OR 12.5 mg or 25 mg suppositories Injection Not recommended for Pediatric Population Adults 75mg **IM (*Should not be given as IV bolus)*** Intravenous Infusion: Diluted with 100-500ml of either sodium chloride solution (0.9%) or glucose solution (5%) then buffered with sodium bicarbonate solution (0.5ml 8.4% or 1ml 4.2%). ***Only clear solutions solutions should be used and for severe pain.***	8hrly 8 or 12 hrly 24Hourly (12 hourly only in severe cases	Tablets 25mg 50mg Slow Release Tablets 75mg 100mg Suppositories 12.5mg, 25mg, 50mg or 100mg. 3ml Ampoule containing 75mg	Not for children <6 months. Maximum: 150mg daily The maximum daily dose of 150 mg should not be exceeded maximum of 3 mg/kg daily, given in divided doses. The maximum daily dose of 150 mg should not be exceeded. The maximum daily dose of 150 mg should not be exceeded. And *should not be given more than two days*

[b] For patients who are on NSAID to check on the hepatoxicity, GIT, Cardiac renal complications.

Table 7: Drugs Used In Pain Management

Oral morphine[e]	0.5mg/kg (max 20mg)	3-hrly	see below	prescribe PRN antiemetic and laxative
Injectable morphine	**Loading Dose IV:** 0.05–0.1mg/kg over 10 minutes.	**Infusion Rates (µ/kg/hr)** 0 – 3 months: 5-10 3 – 6 months: 5-20 >6 months; 10 – 40	**Naloxone for overdose** **Initial Dose:** 10-800 µ/kg IV **Repeat Doses:** 100 µ/kg to a Max of 2mg)/kg IV as a single dose	

Psychosocial Support

SCD is a chronic disease with many challenges to the patient and their families. Patients go through periods of pain, requirements for inpatient care with separation from their families or daily activities, physiological changes in their bodies due to the chronic hemolysis and the potential threat of SCD complications. Parents experience guilt of having passed the sickle cell gene to their child, challenges of watching their children experience the complications of SCD like pain, absenteeism from work as they regularly seek health care for their children and the financial drain of the disease. Adults with SCD sometimes also experience stigma when choosing marital partners and when making career choices. This necessitates that patients and their families are offered psychosocial support within the healthcare system or as part of patient support groups.

Nutritional Support

SCD patients should eat diets with healthy nutritious foods just like other normal children. Parents should be encouraged to give their children plenty of water or fluids. Folic acid supplementation is necessary due to its increased demand from the chronic hemolysis.

Malaria Prophylaxis

SCD patients are susceptible to malaria infection which may have serious consequences. It is recommended that for patients living in high transmission malaria areas or non-immune individuals that prophylactic antimalarial drugs are used in addition to the general precautions (e.g. use of insecticide treated mosquito nets and environmental measures). Patients living in low malarial transmission zones do not require prophylaxis. Below are recommendations of the drugs that can be used for malaria prophylaxis:

[a] Morphine is only available at level 4 and above as well as palliative care centers
[e] For morphine use, check for respiratory distress in children and assess for addiction in adults.

Table 8: Drugs Used In Pain Management

Proguanil			**Mefloquine (5 mg/kg body weight once a week)**	
Under 1 year:	1/4 tablet (25 mg) daily		5-10 kg	1/8 film-coated tablet*
1 to 4 years:	1/2 tablet (50 mg) daily		**10-20 kg**	1/4 film-coated tablet
5 to 8 years:	1 tablet (100 mg) daily		**20-30kg**	1/2 film-coated tablet
9 to 14 years:	1 1/2 tablets (150 mg) daily		**30-45kg**	3/4 film-coated tablet
Over 14 years:	Adult dose daily		> 45 kg	1 film-coated tablet

Routine Clinic Follow Ups

Patients with SCD require to be reviewed regularly at least once every 8-12 weeks. The following algorithms can be used for the first and subsequent clinic visits

First visit for New Patient

Patient history, physical examination and initial laboratory investigations can be conducted as follows:

1. BIODATA AND DEMOGRAPHICS

ONE	Name, Age, Sex, Ethnicity, Physical Address, Telephone contacts, Details of previous health providers; institution, addresses

2. CLINICAL HISTORY

TWO	Ask for history of:	SCD related complications and their frequency Other medical/surgical/maternal health problems Consistency of access to routine/emergency care
	Ask for:	Details of the pain episodes (precipitants,frequency, duration and usual releivers)
	Ask for Detailed Treatment History:	Surgery, Blood transfusion, Drugs in use, Any Allergies, Major complications (stroke, renal failure etc.)
	Ask for family history of:	SCD and other chronic illnesses; diabetes, hypertention etc.
	Ask also for:	Immunization history
	Make a comprehensive review of all the organ systems	

3. COMPREHENSIVE PHYSICAL EXAMINATION

THREE	General:	Weight, height, length/height ploting the BMI SCD facies (frontal and parietal bossing and prominent maxilla) nutritional scores in additional to the conventional signs
	Abdominal Examination:	Inspection, palpation, percusion and ascultation. Examine for palpable splenic and hepatic enlargement
	Nervous System:	SCD facies on the head be observed Examine for focal neurological deficits.
	Cardiovascular System:	Undetertake the standard examination specifically look for right ventricular enlargement
	Respiratory System:	Standard examination but look out for any signs of acute respiratory infection

4. LABORATORY EVALUATION

FOUR	Full blood count (+reticulocytes/peripheralfilm), Blood g G6PD assay if available, Haemoglobinopathy screenrouping,Serum biochemistry, liver enzymes, Hepatitis B & C Abs.

5. ADDITIONAL CARE

A. EDUCATION AND PSYCHOSOCIAL COUNSELLING

A	Concise explanation of the condition and its implications including complications. Genetic counselling (and plans for future children)

B. PROVIDING ADVISORY ON SELF CARE

B	SCD booklet, instructions on how to examine for an enlarged spleen/liver, organise letters for school or employer Introduce and explain use of the SCD Passport

C. ORGANIZING CONTINUING CARE

C	Trans-cranial dopplers (TCDs), Penicillin V and Folic acid, Vaccinations, referral to any other specialist as required, follow-up appointment

Figure 4: Sequence of care provided at follow-up visits

Care to be Commenced at First Visit

Clinical care to be commenced at first visit include: health education on the disease, appropriate drugs and clear plans for all subsequent follow-ups. Their immunization program should also be communicated to cater for routine and SCD specific requirements. The diagram below shows a summary of the care plan

Education	▪ Educate family (including child) on disease causation complications, need to comply with clinic visits and medications ▪ Family issues including siblings and when the child is old enough some reproductive health issues
Drugs*	▪ Folic acid ▪ Malaria prophylaxis if residing in high risk regions ▪ Penicillin V or Erythromycin in cases of penicillin allergy
Vaccinations*	▪ Ensure routine program up-to date ▪ Pneumococcal based on schedule status and age (see below)
Planning future care	▪ Generally, monthly and bimonthly clinic visits are recommended for stable children under 2 and over 2 years respectively. Thereafter visits should be individualized. ▪ The patient can however visit the clinic at ANY TIME for medical, educational or psychosocial concerns

Diagnosed SCD Patient: Follow Up Clinic Visits

Not ALL services listed below need to be provided on each attendance. Always check that the child has had everything done on the new-patient list; due to the nature of a new-patient attendance it is not always possible to have achieved everything at that first appointment.

Comprehensive History	▪ All the components of history included in figure 4 are performed here as well ▪ Encourage these patients or their families to keep diaries of all events between meetings with health providers. This will be helpful in ensuring comprehensive history taking
Physical Examination	▪ Comprehensive examination of all the systems should be done as indicated in figure 4
Blood tests	▪ Full blood count, reticulocytes and film (including HbA:S ratio only if recently transfused) ▪ Haemoglobinopathies screen. This should may be repeated after 1 year of age ▪ Malaria test if history of fever or febrile (Temperature>37.5°C) U+Es, Creatinine, LFTs when necessary at least once a year and when required
Provide / Organize / Prescribe / Check	▪ Document full blood count/ hemoglobin results in SCD booklet. ▪ Penicillin V and Folic Acid, malaria prophylaxis (as indicated by residence) ▪ Reinforce advice on healthy diet, nutrition, hydration, hygiene, prevention of crises and lifestyle choice ▪ Follow-up appointment

Management of Common Emergencies

The Seven-point sequence of emergency management plan on admission of a known case of Sickle Cell Disease

1. Pain Relieve

- Assess Pain Severity
- Review home medications
- Paracetamol 15mg/kg QDS +/- Ibuprofen 5mg/kg/ Diclofenac 1mg/kg TDS

2. Vital signs and Oxygen Saturation Assessment

- Hourly first 6 hours
- 2-4 hourly when stabilized

3. Oxygen Administration

- Within 15 minutes
- Target Saturation >95%

4. Intravenous Access + Bood Tests within 60 Minutes

- Request full blood count result to be available within 1 hour
- Target SatFull blood count, reticulocytes, liver function tests, urea, electrolytes, group & saveuration >95%

5. Blood Cultures + IV Antibiotics – Within 60 Minutes

- If child has fever or fast breathing/ respiratory distress

6.Crossmatch 40ml/kg – Request Within 60 Minutes

- Anticipate transfusion with acute severe anaemia/stroke/ chest syndrome/ girdle syndrome/ splenic sequestration
- Take blood for group & cross match within first hour, then contact lab for urgent blood to be available within 2 hours of call

7.Hydrate IV/ Oral Fluids – Within 60 Minutes

- Document intake and output, review daily
- Oral route if able to drink & IV if poor oral intake or nil by mouth
- Give 1.5x normal maintenance (except if stroke suspected – give 2/3 maintenance

Figure 5: Seven-point sequence of emergency management plan on admission

Pain assessed as mild, moderate or severe (see page 20 and medications administered according to severity (see table 7 page 22-24)

Management of Acute Complications

Fluid Management and Rehydration in Acute Phase

Patients with SCD are at risk of dehydration due to impaired renal concentrating power and poor fluid intake.

1. Adequately hydrate with 150% of the normal daily fluid intake
2. Encourage oral fluids first, it should be used whenever possible
3. Give IV fluids if the patient is unable to drink well, has severe pain, abdominal symptoms, or is not settling
4. Stop IV fluids when the patient is stable, and pain is controlled
5. Maintain a strict input/output chart for every patient
6. Any crystalloids with sugar can be used. In children 5% Dextrose + 0.45% saline is preferred with a review needed for added potassium as per the Basic Paeditric Protocols 2016 for fluid management.

Fluid Calculations

Table 9: Fluid Calculations

Body weight (kg)	Fluids (ml/kg/day)
0 - 10 kg	150ml/kg/day
11 – 20kg	75ml/kg/day for every kilogram above 10kg ADDED TO 1500ml for the first 10kg of weight
> 20kg	30ml/kg for every kilogram above 20kg ADDED TO 225OML for the first 20kg of weight
Divide the total daily volume by 24 hours to obtain hourly fluid rate. CAUTION IN STROKE OR ACUTE CHEST SYNDROME there is risk of cerebral or pulmonary edema respectively. Therefore, do not overload with fluids. Initially give half of the volumes in the table. Reassess hydration status regularly, modify fluids accordingly	

Fever

Patients with Sickle Cell Disease frequently present with fever as the only predominant symptom and sign. While evaluating them, it is important to note that they are at risk of overwhelming septicaemia with encapsulated organisms due to loss of normal splenic function. The most important organisms are *Pneumococcus, Salmonella spp, Haemophilus influenzae type B, and Escherichia coli.*

Differential Diagnosis

Focus fever: Respiratory Tract, Urinary Tract Infection , Central Nervous System, Bone, Joint, Generalized septicemia, Malaria infections as well as Acute chest syndrome.

Laboratory Tests

Undertake appropriate laboratory work as per existing guidelines and geographical region.

Management

1. Oxygen therapy if needed as per guidelines (to keep SaO2 >95%)
2. Antibiotics appropriate to focus, OR if unknown focus then broad-spectrum antibiotic + antimalarial according to existing guidelines for treatment of infections.
3. Fluids oral/ Intravenous IV
4. If chest syndrome is suspected institute appropriate regime
5. Always ensure immunizations and prophylactic penicillin status at discharge

Acute Chest Syndrome

This is one the most severe and life threatening of the acute complications. It may often presents like pneumonia with features suggestive of Acute Respiratory Distress Syndrome (ARDS)

Clinical Presentation

1. Cough, Wheeze, Fever, Tachycardia
2. Acute chest pain worse with breathing
3. Respiratory distress with clinical signs of consolidation
4. Hypoxia (SaO2 <95% on air) and/or Cyanosis

Treat as chest crisis if >1 of these is present.

Investigations

1. Haemoglobin and full blood count
2. Blood group and Crossmatch
3. Chest Xrays
4. Arterial blood gas if in respiratory failure

Management

1. Admit the patient for monitoring
2. Supplemental oxygen to maintain SaO2 >95%
3. Analgesia as per protocols
4. Fluids IV according to hyper hydrate protocol,
5. Antibiotics using guidelines for treatment of severe pneumonia
6. Blood transfusion (10ml/kg red blood cells) if haemoglobin concentration is >1.0 g/dl below baseline.

Severe Anaemia/Haemolysis

This is when Hb is below 5g/dl or acute drop of more than 2g/dl from baseline or acute drop in Hb >2g/dl below steady state. It is often precipitated by: Malaria/bacterial infection, Splenic sequestration, Haemolysis and Bleeding (gastrointestinal tract, menstrual bleeding, open wounds).

Clinical Presentation

1. Symptoms of low Hb and/or hypovolemia (feeling weak, tired, breathlessness, palpitations)
2. Jaundice
2. Cinical signs of shock (tachycardia, hypotension) or cardiac failure
3. Splenomegaly
4. Hepatomegally

Investigations
1. Blood Group & Cross-Match
2. Full blood count
3. Renal function tests
4. Liver function tests
5. Lactate Dehydrogenase
6. Urine microscopy
7. Random Blood Sugar
8. Urine urobilinogen
9. Blood cultures
10. Malaria parasites
11. G6PD screen

Management
If haemolysing:
1. Transfuse immediately if symptomatic or Hb <5g/dl
2. Top-up to steady state level if asymptomatic and Hb >5g/dl

If aplastic:
1. Transfuse immediately if symptomatic or Hb <5g/dl
2. Whole blood: 20mls/kg or Packed RBC 10mls/kgm

*Reticulocyte count helps differentiate hemolysis from aplastic crisis. They are raised in the former and reduced in the latter

Sequestration Crisis

Splenic sequestration is another common and serious manifestation during the pre-autosplenectomy phase of the illness. It caused by pooling of blood in enlarged spleninc vascular bed often resulting from infections or other stressful events.

Clinical Presentation
1. Severe Pallor
2. Lethargy
3. Hypotension, tachycardia, hypovolaemia
4. Abdominal pain and distension
5. Fever
6. Increasing splenomegaly

Investigations
1. Blood Group & Cross-Match
2. Full blood count
3. Renal function tests
4. Liver function tests
5. Lactate Dehydrogenase
6. Urine microscopy
7. Random Blood Sugar
8. Blood cultures
9. Malaria parasite

Management
1. Admit for observation, monitoring and if in shock provide 20ml/kg bolus normal saline whilst awaiting blood
2. Top-up to baseline Hb immediately (within 3 to 4 hours of admission)
3. Administer broad spectrum antibiotics as per existing guidelines
4. Fluids oral/ IV
5. Oxygen to keep SaO2 >95%
6. Analgesia as indicated according to the guidelines.

Note: Splenic sequestration is one of the commonest causes of death in children below 2 years of age. It is most common in infants and children and tends to be recurrent. Hepatic sequestration can also occur, usually in children above 4 years old.

Neurological

These usually present as strokes and or seizures but may also appear in form of subtle neurological manifestations including learning, concentration disorders among others. Strokes may be ischaemic or haemorrhagic. Ischaemic stroke is most frequent in children and in adults between 35 and 65 years of age while haemorrhagic stroke is most frequent in young adults and has a high case–fatality rate. They frequently appear as complications of other SCD crises.

Presentation
1. Change in neurological status (weakness/slurred speech/ blurred vision/behavior change/altered consciousness/seizure)
2. Headache
3. Raised Intracranial Pressure (ICP), bradycardia, hypertension, sluggish pupils
4. History of previous stroke

Investigations
1. Blood Group & Cross-Match
2. Full blood count
3. Blood cultures
4. Malaria parasite
4. CT or MRI

Admit and monitor;
1. Hourly Glasgow Coma Scale (GCS)
2. Vital signs (BP, Pulse, RR, SO_2 Saturation)
3. Hydrate with upto to 60% maintenance

Perform
Exchange transfusion within 4 hours of admission or if delay expected then give top-up transfusion within 4 hours aiming to achieve HbS <30%. This can be repeated depending on neurological status and HbS level

Supportive care (as indicated)
1. Antibiotics or Acyclovir for Bacterial or viral meningitis
2. Antimalarials as necessary
2. Anticonvulsants for convulsions
3. Dexamethasone for increased intracranial pressure

Priapism

A persistent penile erection that continues hours beyond or is unrelated to sexual stimulation. In childhood, males with SCD need to know that priapism is one aspect of SCD and they should tell their parents or guardians/doctor if it occurs. If this condition is untreated it can result in impotence in the future. It can be triggered by sexual activity or full bladder

Presentation
1. Acute, fulminant (cases lasting longer than 4 hours),
2. Stuttering (repeated painful erections lasting more than 30 minutes and up to 4-6 hours)
3. History of previous stroke

At the initial evaluation
1. Document the time of onset of the episode
2. Document precipitating factors e.g. trauma, infection, use of drugs (e.g. alcohol, psychotropic agents, sildenafil, testosterone, cocaine)

Further Steps
1. Increase fluid intake
2. Analgesia and anxiolytic agents e.g diazepam
3. Catheterize and attempt micturition
4. Walking and warm baths may also help avert early priapism

Refer
For episodes lasting more than 2 hours, patient should be transferred directly to the referral hospital with senior practitioners able to provide the necessary haematological and urological interventions

Advanced care by specialists
1. Exchange transfusion
2. Surgical intervention

TO BE UNDERTAKEN BY APPROPRIATELY SKILLED EXPERTS ONLY

Management of Chronic Complications

Hypersplenism

Chronic splenic sequestration associated with enlarged spleen with anaemia and reduction in white blood cells and platelets. This anaemia is usually chronic in nature and patients rarely present with signs of heart failure.

Presentation
1. Pallor
2. Lethargy
3. Abdominal distension
4. Chronic splenomegaly

Investigations
1. Full blood count, Reticulocytes, Peripheral smear
2. Creatinine, Urea, Electrolytes, Liver Function Tests
3. Lactate Dehydrogenase
4. Blood cultures, Malaria rapid test & microscopy
5. Serum Iron studies
6. Bone marrow aspirate

Management I
1. Assess and document size of liver and spleen mark on abdomen
2. Exclude and/or treat all other causes of anemia

Management II
Review after 3 months monitoring spleen size and document at every visit

Further Management
1. Refer to surgical department for elective splenectomy if no change and evidence of hypersplenism persists
2. Therapeutic splenectomy is also indicated if more than 2 episodes of sequestration

Orthopaedic

The most common orthopaedic complications of SCD are related to vaso-occlusion (avascular necrosis) or infections (osteomyelitis and septic arthritis)

Avascular Necrosis

Pain in the hip or groin referred to leg or knee on movement; later at rest, repeated or prolonged pain for more than 8 weeks should be investigated for aseptic necrosis. Proximal humeral changes may be seen in shoulders as an incidental finding on CXR. Limitation of movement particularly; abduction, external rotation of the hip joint and external rotation of the shoulder.

Differential diagnosis
Osteomyelitis/Septic arthritis suggested by pyrexia, systemic illness and positive blood cultures

Investigations
X-ray
MRI

Supportive Management
1. Non-steroidal anti-inflammatory agents ± codeine derivatives
2. Rest
3. Avoid bearing weights

Definitive Management
Refer to orthopaedic surgeon

Osteomyelitis/Septic Arthritis

The diagnosis of osteomyelitis in the context of SCD differs slightly from the general population in microbiology. Though the ranking of bacterial aetiology is the same, Salmonella is more frequent in this group. Presents with: unusual swelling and/or pain, fevers and persistent signs of inflammation around the site (redness, tenderness, warmth, swelling).

Investigations
1. Full blood count, CRP , ESR, Blood cultures
2. X-Ray, Ultra sound and MRI of affected bone
3. Joint aspiration

Differential Diagnosis
Avascular necrosis

Management I
A decision is taken to treat for osteomyelitis appropriate antibiotics should be chosen according to prevailing guidelines

Management II
Refer to orthopaedic surgeon

Renal and Ophthalmic

Renal and ophthalmological complications, capable of threatening quality of life and/or causing death are seen in long standing disease.

Renal Complications

Renal involvement can occur throughout the life of an individual with sickle cell disease

Common manifestations of Sickle Cell Nephropathy
1. Hyposthenuria (urine concentration abnormalities)
2. Microalbuminuria or proteinuria
3. Haematuria
4. Acute or Chronic Kidney Disease and End-stage Renal Disease
5. Medullary Carcinoma

Recommended diagnostic tests before referral
1. Urine for Microalbuminuria
2. 24-hour urine protein determination if proteinuria
3. 24-hour urine creatinine clearance
4. Serum Electrolytes.

Management
Should be referred to appropriate experts to manage as per existing guidelines

Ophthalmic Complications

Ophthalmic complications can occur any time in life but are more often seen after the age of 10 years.

Ophthalmic complications are relatively common and may occur in any vascular bed of the eye and may not be detected at their early stages unless an eye examination is performed annually. An INDIRECT fundoscopy should be done at least once a year. Examination of the fundus should be performed annually.

This examination can be done by a specialist ophthalmologist or a clinical officer with additional one-week training on indirect fundoscopy. Currently, the following facilities have this service: Sabatia Eye Hospital, Tenwek Hospital, Kenyatta National Hospital, Light House Mombasa and Kwale Eye Centre.

1. If there is no sickle cell retinopathy, annual check ups suffice
2. Check ups every 6 months are recommended if there is non-proliferative sickle cell retinopathy,
3. Monthly check ups are recommended for proliferative sickle cell retinopathy.

If ophthalmic complications are identified or suspected the patient should be referred to the nearest ophthalmology services available.

Screening for Chronic Complications

Sickle cell disease may manifest with many complications. The most frequently encountered chronic complications and monitoring strategies are summarized in figure 6. These should be undertaken by relevant experts at the times specified in the figure.

Renal disease	▪ From age 10 years screen for proteinuria at least once a year. ▪ If positive perform a first morning void urine albumin-creatinine ratio / 24-hour urine creatinine clearance and if abnormal, consult with or refer to a renal specialist
Hypertension	▪ In adults screen for hypertension and treat to lower systolic blood pressure ≤140 and diastolic blood pressure ≤90. ▪ This should be scaled in line with the norms in children
Cardiac Disease	▪ Comprehensive clinical cardiology reviews every year ▪ Relevant tests including Echocardiography should be determined by reviewing clinicians
Pulmonary hypertension	▪ Regular clinical evaluation for cardiorespiratory symptoms ▪ Regular pulse oximetry (PO_2); screening ECHO starting at the age of 3 years; repeat 5 yearly
Retinal Disease	▪ Retinopathy screening should be performed commencing at age 10 years then every 1-2 years thereafter. ▪ If suspicious for retinopathy refer to a retinal specialist
Central Nervous system (stroke)	▪ Annual screening with Transcranial Doppler (TCD) ultrasound from 2 years to 16 years ▪ After 16 years of age continue with annual screening using CT or MRI scans.
Iron overload	▪ Maintain record of volume of RBC transfansfusions ▪ In chronically transfused, measure serum ferritin 3 monthly

Figure 6: Approach to screening for chronic Complications during follow-up

Sickle Cell Disease in Reproductive Health

Sickle Cell Disease adversely affects the course of pregnancy, childbirth and puerperium. It is therefore important that men, women and mothers are aware of SCD and its effects on their reproductive health.

Educational and health promotion counseling should be provided to all women and men of childbearing age to reduce reproductive risk and improve pregnancy outcomes. Trained healthcare workers should undertake counselling on health promotion and prevention of complications arising from sickle cell disease, childbirth and thereafter. Where the partner of a man or woman with SCD has unknown SCD status, a screening/test for haemoglobinopathy should be carried out at the nearest health facility offering that service. After testing, couples who are at risk for having a potentially affected fetus and neonate should be referred to a specialist for genetic counseling and care.

In women with SCD, regular use of contraception can decrease the health risks associated with an unintended pregnancy.

- **Progestin**-only contraceptives (pills, injections, and implants), levonorgestrel IUDs, and barrier methods have no restrictions or concerns for use in women with SCD.
- **If the benefits are considered to outweigh the risks, combined hormonal contraceptives (pills, patches, and rings) may be used in women with SCD.**

Pregnancy in women with SCD is considered high risk; there is an increased risk of adverse pregnancy outcomes including intrauterine growth restriction, pre-term delivery and still birth. Risks to the mother include an increased frequency of pain crises and an increased risk of thrombosis, infections, pre-eclampsia and death in comparison to women who do not have SCD[12]. It is therefore important that a woman with SCD be seen prior to conception and be followed throughout pregnancy, childbirth and puerperium to improve pregnancy outcomes for the mother and baby.

a. Pre-conceptual counseling should include:

Partner screening for haemoglobinopathies, analgesic dependency, transfusion history, discussion of mode of delivery, immunization history and neonatal screening.

b. Investigations

Beyond the minimum prenatal profiles these patients should have the following:

i. Haemoglobin level at every clinic visit
ii. Urea and electrolytes to screen for sickle cell nephropathy
iii. Screening for red cell allo-antibodies
iv. Echocardiogram, if possible, to screen for pulmonary hypertension.

c. Ante-natal Management

i. Folic acid should be given once daily both pre-conceptually and throughout pregnancy. If there is laboratory confirmation of iron deficiency by serum iron levels, iron should be prescribed
ii. Hydroxyurea should be stopped at least three months before conception
iii. Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers should be stopped before conception
iv. Women with SCD should be considered for low dose aspirin 75mg once daily from 12 weeks of gestation and be advised to receive prophylactic low molecular weight heparin during antenatal admissions
v. Persistent vomiting with dehydration increases the probability of a sickle cell crisis, therefore they should be advised to seek medical attention early.

[12]Segbena AY, Guindo A, Buono R, Kueviakoe I, Diallo DA, Guernec G, et al. Diagnostic accuracy in field conditions of the sickle SCAN® rapid test for sickle cell disease among children and adults in two West African settings: The DREPATEST study. BMC Hematol 2018;18:1–10. doi:10.1186/s12878-018-0120-5. Kutlar F. Diagnostic approach to hemoglobinopathies. Hemoglobin. 2007;31(2):243-50.

d. Intra-partum management[13]

i. Women with SCD should be advised to give birth in hospital where a haematologist is available
ii. At 38+0 weeks, an elective normal delivery can be induced or elective caesarean surgery if indicated
iii. Opiate analgesia except Pethidine can be used to complement regional analgesia for caesarean sections
iv. Adequate hydration must always be maintained
v. Oxygen saturation should be sustained at above 94% during delivery
vi. Perioperative complications of surgery in SCD patients include hypoxia, dehydration, bone pain crisis, significant anemia, and acute chest syndrome
vii. Prophylactic antibiotics must be given on time and therapeutic doses should be given early enough to avoid complications arising from especially atypical bacteria and/or nosocomial infections
viii. Other strategies to improve perioperative outcomes in SCD include conservative preoperative blood transfusion therapy, epidural analgesia, adequate postoperative pain control with opiate and non-opiate analgesia.

A woman who is pregnant and has Sickle Cell Disease should be followed up at a level 3 or 4 facility. Proper follow up should be adhered to and advise on what can be done at primary facilities. HCWs at the facilities need to be capacity build to identify symptoms, care for patients and empower for referral.

Haemoglobinopathy Screening

Screening programmes include pre-marriage/preconceptual, antenatal and neonatal programmes. In addition, targeted screening for sickle cell haemoglobin may be carried out in other circumstances like: before anaesthesia for a person in high endemic area; for sportsmen and for recruitment into the disciplined forces. The aim is to either reduce the effects of a condition or to lessen the number of births of a baby with a serious disorder (by offering information about carrier status prior to marriage or conception).

Screening should be socially and ethically acceptable to the community served, health care workers involved, individuals identified as carriers and their families. Potential benefits should outweigh any potential harm. The quality of counselling is very important in avoiding adverse social effects. Imparting information as to carrier status has been found to be more acceptable to the people concerned if they are also informed of the potential benefits of being a carrier. For example, in the case of β thalassaemia trait, not just the partial protection from falciparum malaria but also protection against coronary artery disease and ischemic cerebrovascular accidents [14]

Neonatal Screening

Neonatal screening, when linked to timely diagnostic testing, parental education and comprehensive care, markedly reduces morbidity and mortality from SCD in infancy and early childhood. All children presenting with unexplained acute illness, including acute pain in any part of the body, anaemia, acute neurological symptoms, loss of vision, collapse, respiratory symptoms, hepatosplenomegaly, jaundice, swollen limbs and sepsis should be tested for SCD. If screening is missed at birth, then it should to be done at first contact with the system .

Premarital, Antenatal and Postnatal Screening

Patient's relatives and youths are encouraged to screen for their status. Family trees should be used to link the potential carriers and SCD patients.

[13]NICE guidelines on Management of Sickle Cell Disease in Pregnancy. July 2011. Available at https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_61.pdf accessed on 10th April 2020
[14]Bain BJ. Haemoglobinopathy diagnosis: Algorithms, lessons and pitfalls. Blood Rev 2011; 25:205–13. doi: 10.1016/j.blre.2011.04.001.

Psychosocial Counseling

The Health Care Providers

A trained counsellor should be able to perform this task. Although they are few, capacity building will be done to train others to provide this service. This can be achieved with laypersons and paraprofessionals. Individuals selected for this task must possess certain personal qualities including good communication skills, engaging personality and the discipline to limit information transmission to what has been approved for them to provide.

Identifications of Different Needs

Children and teens with SCD and their families may need academic and vocational guidance as well as advice on recreational activities and travel. The basic premise is that parents should treat their affected child as normally as possible and they should encourage activities that foster self-esteem and self-reliance. These feelings will help children and adolescents to cope more effectively with their illness. Educational materials should be provided to teachers and other school officials who interact regularly with children with SCD. School personnel should meet with the parents to set realistic educational goals. Illness often interrupts schooling and extracurricular activities, so tutoring or other assistance may be needed. Unless impaired by cerebrovascular disease, children with SCD have normal intelligence and should be encouraged to reach their full potential. Vocational counseling is important for adolescents and adults with SCD. The long-term goal is to prepare the child with SCD for independent living. Introducing children and adolescents to adults with SCD who have coped successfully with their illness has a positive effect.

Prenatal

Availability of prenatal diagnosis offers the family choices regarding the continuation of pregnancy. When decision is made to continue, the practitioner has time to assist the family in preparing for the arrival of a child with SCD. This time must be spent educating the parents and family about the disease and the need for family and community support. The better educated the family and the community, the better care the patient will receive. Many communities have SCD support groups that provide an avenue for sharing anxieties as well as helpful information. Whenever possible, satisfactory housing, accessible optimal medical care and reliable transportation must be planned before the baby arrives.

Infancy

Health insurance, emergency transportation, housing and anxiety about recognizing symptoms are some of the issues new parents may need help acknowledging and addressing. Frequent clinic visits and home visits will allow the opportunity for parents and providers to establish a comfortable relationship to address these issues and help establish an ongoing pattern of compliance. Although advances in medical research have increased the chances for longevity, lack of understanding on the part of providers may result in inappropriate treatment plans that defy adherence. The establishment of clinical practice guidelines in SCD has decreased but not eliminated preventable deaths. In addition, non-compliance may undermine the best care plans.

Travel, Sports and Fun Activities

Patients should be encouraged to exercise regularly on a self-limited basis. School-age children should participate in physical education but they should be allowed to rest if they tire and encouraged to drink fluids after exercise. The potential risks of strenuous exertion should be discussed with the patient.

Children and adolescents may engage in competitive athletics with caution because signs of fatigue may be overlooked in the heat of competition. Coaches are advised against blanket exclusion from participation or excessive demands for athletic excellence. Patients with SCD should dress warmly in cold weather and avoid swimming in cold water. Patients or families should seek advice on the best modes of travel. Flying in pressurized aircrafts usually poses no problems for sickle cell patients. However, they should dress warmly to adjust for the cool temperature inside, drink plenty of fluids and move about frequently when possible. On the other hand, travel above 15,000 feet in non-pressurized vehicles, mountain climbing, hiking or deep sea diving or staying under water without breathing (static apnea) can induce vaso-occlusive complications. Ordinary travel by car, bus or train is not associated with increased risk of complications although frequent rest and refreshment is good.

Transition to Adolescence

Adolescence is a difficult time of life for youngsters with chronic diseases. While their peers become independent, teenagers with SCD may need frequent help due to illness. They can become frustrated and have trouble expressing their feelings. Concern about issues such as body size, sexual function, pain management and death often is expressed as rebellion, depression or refusal to heed treatment.

Adolescents should be advised not to use tobacco, alcohol and illegal drugs. Post pubertal adolescents should be educated about sexuality, safe sex practices and use of condoms to prevent sexually transmitted diseases.

Girls should be counseled about the risks of pregnancy in women with SCD, safe birth control practices and merits of pregnancy at the right age and social circumstances. Adolescents may view their long-time pediatric health care providers as too close to their parents and not speak frankly to them. In this case, families could be referred to adolescent medicine specialists to discuss sensitive issues and prepare for adulthood. Alternatively, adolescents may be more open to express their concerns through "teen support groups."

Service Delivery

The organization of levels of care for SCD shall be aligned to the existing health care service delivery structures as per the table below.

Table 10: The structure of service delivery and care levels

HEALTH SECTOR (PUBLIC AND PRIVATE) FACILITY CATEGORIZATION[15]		SCD CARE LEVELS	SERVICES TO BE PROVIDED
I	**Community**	**SCD Care Level 1**	**Health Promotion on Sickle cell**
II	Dispensary/medical clinics/mobile clinics		All services for **Level 1 plus** 1. Case identification, basic treatment, medication compliance, some rehabilitation, advising on safe home drug storage service integration and referral 2. Ensure they maintain the personal diary or notebook 3. Specimen referral for confirmatory tests (Dry Blood Sample (DBS))
IIIA	Basic Health Centre		All the services for **Level II plus** 1. Full blood count 2. Genetic Counselling 3. Rehabilitation services including physiotherapy
IIIB	Comprehensive Health Centre//Nursing home etc		All services for **Level IIIA plus** Provision of Hydroxyurea.
IV	Primary Referral (County)	**SCD Care Level 2**	All services for **Level IIIB plus** 1. Emergency care of SCD and its complications. 2. Enhanced Laboratory Capacity to cover all support care and monitoring tests

[15] Based on Facility_Classification_2020_Vol.CXXII-No_.24

Table 10: The structure of service delivery and care levels

V	Secondary Referral (Regional/County) Facilities	SCD Care Level 3	All services offered at Level IV 1. Comprehensive care facilities providing more advanced laboratory and comprehensive clinical care 2. Confirmatory diagnosis (HPLC, Iso-electrophoresis,) 3. Transcranial Doppler (TCD) testing

Detailed structure of the Health Systems Supporting National SCD Care Program

Care Level 1: The Primary Health Care
The facilities at this level include communities, dispensaries and the health centres. The care offered here shall be basic. These shall mainly be identification of persons with sickle cell disease in the community and referral to the next level of care. The players shall include community members, community health workers and nurses whose responsibility is to identify, use a family tree to map out the likely patients and provide basic health care as per CHW package, physiotherapy, psycho-social support and health education.

Care Level 2: Satellite Treatment Centres
All the primary 47 County referral hospitals are in this category. Treatment and follow up will be provided in all these hospitals. All the identified and mapped satellite treatment centres will be linked vertically to the more advanced County referral hospitals and horizontally. The technical level of expertise shall require a nurse, medical doctor, dentist, pharmacist, clinical officer and physiotherapist trained to care for persons with sickle cell disease. A consultant medical specialist, paediatrician, physician or other equivalents should provide leadership and coordinate the activities within the county.

Care Level 3: Mid-level care/ Intermediate Centres/ Comprehensive Care Centres
These are Regional County referral facilities that are slightly more equipped. These shall be more capacitated and located in hot spot areas with staff that shall provide additional laboratory and clinical care. Treatment and follow up will also be provided in these centres on case by case basis.

Care Level 4: Advanced Care Centres
Advanced level of care centres shall be able to handle complicated cases, specialized treatment and routine follow-up on case by case basis. Currently, Moi Teaching Referral Hospital and Kenyatta National Hospital are the only facilities providing advanced Sickle Cell Disease care. To increase accessibility, Coast General Hospital and Jaramogi Oginga Odinga Referral Hospital shall be included to this level of care to serve more regions.

Centres of Excellence
SCD Centres of Excellence shall be established. They will be dedicated centres that will offer comprehensive care for SCD as offered in Level 4 care. Additionally, they should be able to perform research and training of subspecialists for SCD care alongside provision of advanced care such as stem cell and bone marrow transplants. These shall be Kenyatta National, Kenyatta University Teaching and Moi Teaching and Referral Hospitals.

Annexes

Annex 1: Preparation for Surgery

Investigations to be performed prior to admission for transfusion are:

i. Full blood count
ii. HbS % level if recently transfused or on regular transfusion from HPLC available from SCD laboratory team
iii. Cross-match to ensure that extended RBC phenotype is already known
iv. Urea, electrolytes, creatinine and liver function tests
v. Ferritin if transfused regularly

Operative Preparation

Informed consent is needed from the care giver in liaison with a Haematologist/physician as directed in the national transfusion guidelines.

Do not attempt to raise the haemoglobin level by more than 4 g/dl at any one transfusion. The usual rate of transfusion is 2-3ml/kg/hour and for elective transfusion, should never exceed a maximum rate of 150 ml/hour. For post-transfusion, check full blood count and HbA/S ratio. Additional annual investigations include HBsAg, level of anti-HBs Ab (revaccinate if less than 100 IU/ml) , HCV Ab and HIV.

Preliminary Investigations:

i. Full blood count
ii. HbS % level (not urgent at first exchange)
iii. Cross-match approximately 30mls/kg (average unit contains 220 -250mls)
iv. Request exchange transfusion blood from laboratory. It will need to be ABO, Rh and Kell matched and sickle negative
v. Urea, electrolytes, creatinine, liver function tests and Calcium
vi. Arterial blood gases in patients with symptoms suggestive of ACS or girdle syndrome

Annex 2: Iron Chelators to be Considered During Transfusion

Overview

Based on available evidence [16&17] on Desferrioxamine (DFO), Deferiprone (DFP), Deferasirox (DFX), combination of DFO and DFP should be made available as treatment options for patients who have Sickle Cell Disease and have iron overload caused by transfusions.

Desferrioxamine (DFO)

Can be used from the age of 2 years and is administered parenterally (subcutaneous infusions 8-12 hours of a 10% DFO solution, using an infusion pump for at least 5 days per week). Recommended starting point is when the serum ferritin levels reach 1000 µg/L or after the first 10-20 transfusions due to the fears that toxicity would have on growth of ears and eyes at low levels of body iron.

Standard dosing is 20-40 mg/kg for children and up to 50-60 mg/kg for adults per day. For rescue therapy where iron overload has already happened, doses of over 50 mg/kg are required to achieve negative iron balance.

Deferiprone (DFP)

Can be used from the age 6 years and is administered orally at 75 mg/kg/day, given in three doses. Each 500 mg tablet is scored to facilitate tablet splitting. An oral solution is also available for paediatric use. Adjustments may be made based on the patient's response but should never exceed 33 mg three times daily.

Deferasirox (DFX)

Can be used from the age of 2 years and is administered as an oral suspension preferably before meals. It is used as a first-line monotherapy in many countries. A starting dose of 20 mg/kg is recommended for patients who have received 10-20 transfusion episodes and currently receive standard transfusion at rates of 0.3-0.5 mg of iron/kg/day. For normal transfusion use more than 0.5 mg/kg/day. In patients with pre-existing high levels of iron loading, use of 30 mg/kg/day is recommended. Higher doses of up to 40 mg/kg/day are recommended for rescue therapy that can be divided into two daily doses.

Combined DFO and DFP

Combinations of these two drugs are useful, especially when various monotherapy regimes have failed to control either liver iron or cardiac iron. In general, if a patient is not doing well with DFP monotherapy, combined treatment offers an additional option to improve iron balance. Specialist haematologist should work with a clinical pharmacist for dose calculations and adjustments.

See table 11 for specific guidance[18]

[16]Clinical Commissioning Policy: Treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias. NHS guidance August 2016

[17]Ballas SK, Zeidan AM, Duong VH, DeVeaux M, Heeney MM. The effect of iron chelation therapy on overall survival in sickle cell disease and beta-thalassemia: A systematic review. Am J Hematol 2018;93:943–52. doi:10.1002/ajh.25103.

18Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) [Internet]. 3rd edition. Cappellini MD, Cohen A, Porter J, et al., editors. Nicosia (CY): Thalassaemia International Federation; 2014. Chapter 3: IRON OVERLOAD AND CHELATION John Porter, Vip Viprakasit, and Antonis Kattamis.

Table 11: Indications and contraindications for Iron chelators.

Characteristic	DFO	DFP	DFX
Age 2- 6 years	Recommended	NOT RECOMMEND	Recommended
Over Age 6 years	Recommended	Recommended	Recommended
Route of administration	Subcutaneous/Intramuscular/Intravenous	Oral (tablet or liquid)	Oral (dispersible tablet)
Dosage and frequency	20 - 60 mg/kg 5 to 7 times per week	75-100 mg/kg/day in 3 divided doses daily	20-40 mg/kg/day once daily.
Contraindications	Pregnancy (but has been used in 3rd trimester) Hypersensitivity	Pregnancy History of neutropenia or condition with underlying risk of cytopenia Hypersensitivity including Henoch Schönlein purpura: urticaria and periorbital oedema with skin rash	Pregnancy Hypersensitivity Estimated creatinine clearance <60 ml/min Hepatic impairment or renal failure
Watch out for	Monitor ferritin: if it falls to <1000 µg/L, reduce dose (so mean daily dose/ferritin remains <0.025) Monitor audiometry regularly, particularly as ferritin falls Monitor eyes regularly including electroretinography if on high doses Fever suggestive of septicemia with organisms that used ferrioxamine (yersinia, klebsiella) Renal failure or diminishing renal function with other comorbidities	Measure neutrophil count (ANC) before starting and monitor ANC weekly For neutropenia: ANC < 1.5 × 10^9/L) interrupt treatment For agranulocytosis (ANC < 0.5 × 10^9/L), consider hospitalization Advise patients to report immediately symptoms of infection: Interrupt if fever develops Monitor for symptoms of arthropathy	Monitor creatinine trends for 1st 4 weeks after starting or after dose escalation then monthly If rapid fall in serum ferritin to <1000 µg/L-dose reduce. If ferritin 500 µg/L consider very low doses^ Proteinuria may occur occasionally with renal tubular acidosis. Monitor urine protein regularly Prescribing to the elderly: non-fatal gastrointestinal bleeding, ulceration, and irritation may occur caution with

Editorial Team

1. Prof. Fred N. Were, The Kenya Paediatric Research Consortium & Department of Paediatrics and Child Health , University of Nairobi
2. Prof. Jessie N. Githanga, Department of Human Pathology, University of Nairobi
3. Dr. Fredrick Okinyi, Lecturer, Department of Human Pathology, University of Nairobi
4. Dr. Fridah A. Govedi, Ministry of Health
5. Dr. Jamlick Karumbi, Ministry of Health
6. Dr. David Githanga, The Kenya Paediatric Research Consortium & Nairobi Hospital
7. Dr. Bernhards Ogutu, Kenya Medical Research Institute
8. Ms. Irene Amadi, The Kenya Paediatric Research Consortium
9. Mr. James Wanda, The Kenya Paediatric Association

Scientific Reviewers

1. Dr. Doreen Karimi Mutua, Paediatric Haemato-Oncologist, Gertrude's Hospital
2. Dr. Matilda Ongondi, Adult Haemato-Oncologist, Kenyatta National Hospital

Industry Contributors to Manuscript Development

1. Dr. Nathan Mulure, Novartis
2. Dr. Tigist Gebre, Novartis

Graphic Designer & Developer

1. Mr. Kamau Thibitie

References

1. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ 2008; 86: 480–87.

2. Uyoga S, Macharia AW, Mochamah G, Ndila CM, Nyutu G, Makale J, et al. The epidemiology of sickle cell disease in children recruited in infancy in Kilifi, Kenya: a prospective cohort study. Lancet Glob Heal 2019;7:e1458–66. doi:10.1016/S2214-109X(19)30328-6.

3. Amendah DD, Mukamah G, Komba A, Ndila C, Williams TN. Routine Paediatric Sickle Cell Disease (SCD) Outpatient Care in a Rural Kenyan Hospital: Utilization and Costs. PLoS One 2013;8:1–6. doi:10.1371/journal.pone.0061130.

4. Mulumba LL, Wilson L. Sickle cell disease among children in Africa: An integrative literature review and global recommendations. Int J Africa Nurs Sci 2015; 3:56–64. doi: 10.1016/j.ijans.2015.08.002.

5. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN (2013) Global Burden of Sickle Cell Anaemia in Children under Five, 2010–2050: Modelling Based on Demographics, Excess Mortality, and Interventions. PLoS Med 10(7): e1001484. https://doi.org/10.1371/journal.pmed.1001484

6. WHO. Sickle-cell anaemia Report by the Secretariat. 2006.

7. Christopher M. Wanjiku, Festus Njuguna, F. Chite Asirwa, Samuel Mbunya, Cyrus Githinji, Christopher Roberson, Anne Greist; Establishing care for sickle cell disease in western Kenya: achievements and challenges. Blood Adv 2019; 3 (Supplement 1): 8–10. doi:

8. Otieno W, Estambale B, Aluoch JR, et al. Association between Sickle Cell Trait and Low Density Parasitaemia in a P. falciparum Malaria Holoendemic Region of Western Kenya. IJTDH. 2012;2:231–40

9. Uyoga S, Macharia AW, Mochamah G, Ndila CM, Nyutu G, Makale J, et al. The epidemiology of sickle cell disease in children recruited in infancy in Kilifi, Kenya: a prospective cohort study. Lancet Glob Heal 2019;7:e1458–66. doi:10.1016/S2214-109X(19)30328-6.

10. Segbena AY, Guindo A, Buono R, Kueviakoe I, Diallo DA, Guernec G, et al. Diagnostic accuracy in field conditions of the sickle SCAN® rapid test for sickle cell disease among children and adults in two West African settings: The DREPATEST study. BMC Hematol 2018;18:1–10. doi:10.1186/s12878-018-0120-5.

11. Kutlar F. Diagnostic approach to hemoglobinopathies. Hemoglobin. 2007;31(2):243-50

12. Jain D, Atmapoojya P, Colah R, Lodha P. Sickle Cell Disease and Pregnancy. Mediterr J Hematol Infect Dis. 2019;11(1):e2019040. Published 2019 Jul 1. doi:10.4084/MJHID.2019.040.

13. NICE guidelines on Management of Sickle Cell Disease in Pregnancy. July 2011. Available at https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_61.pdf accessed on 10th April 2020

14. Bain BJ. Haemoglobinopathy diagnosis: Algorithms, lessons and pitfalls. Blood Rev 2011; 25:205–13. doi: 10.1016/j.blre.2011.04.001 Clinical Commissioning Policy: Treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias. NHS guidance August 2016

15. Clinical Commissioning Policy: Treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias. NHS guidance August 2016

16. Ballas SK, Zeidan AM, Duong VH, DeVeaux M, Heeney MM. The effect of iron chelation therapy on overall survival in sickle cell disease and beta-thalassemia: A systematic review. Am J Hematol 2018;93:943–52. doi:10.1002/ajh.25103.