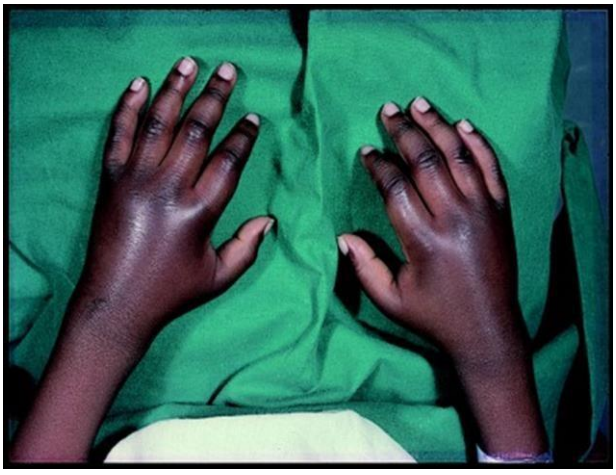
FEDERAL MINISTRY OF HEALTH

Meeting the Health Needs of all Nigerians

NATIONAL GUIDELINE FOR THE CONTROL AND MANAGEMENT OF SICKLE CELL DISEASE (2nd EDITION)



This guideline shall be reviewed and updated every five (5) years or earlier if and when new evidence that should be incorporated arises.

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Images on the Cover Page:

1. Drepanocytes in Sickle Cell Disease. Courtesy: United States National Human Genome Research Institute: Wikimedia.org.
2. Dactylitis in a 14 Months Old Patient with Sickle Cell Disease. Courtesy: Davies SC Oni L BMJ 1997:315:656-660.

FOREWORD

Sickle cell disease (SCD) is one of the top ten (10) non-communicable diseases (NCDs) in Nigeria causing significant morbidity and mortality and consequently undermined the attainment of the Millennium Development Goals (MDGs) 4, 5 and 6. The attainment of the current Sustainable Development Goals (SDG) particularly goals (SDGs) 1, 3, 4 and 10 may be negatively impacted as well if deliberate efforts are not directed toward addressing the disease in our country. This is because SCD is particularly associated with increased poverty, maternal, neonatal, infant and under five mortality which made it a disease of public health importance with greater socio-economic ramifications.

The disease is also occasionally associated with HIV and viral hepatitis (mainly hepatitis B and C) infections due to frequent blood transfusions. Other problems associated with SCD include failure to thrive in children, stunting, stigmatization, job discrimination, illness-related absenteeism from school or work, poverty-related inaccessibility to standard treatment and care, depression, drug dependence and other psychosocial challenges.

Concerned about the enormous challenges caused by SCD, the Federal Ministry of Health (FMOH) in collaboration with the MDG office in 2011 and 2012 empowered six Federal Medical Centers in the six geopolitical zones of the country to run dedicated clinics and programmes for the management and control of SCD and the production of the first edition of this guideline was birthed and published.

Furthermore, the review of the first edition of the national guideline for the control and management of SCD developed in 2011, culminating in the publication of this second edition of the guideline shows government's continuous commitment to reduce not only the burden of SCD but also reduced the morbidity and mortality associated with disease by ensuring that affected individuals receive appropriate clinical interventions in all healthcare facilities nationwide as the guideline still retain it's rich multi-level of healthcare applicability.

I therefore encourage all healthcare providers at all levels of care in our country to take advantage this national guideline provides to improve their standard of care for individuals living with SCD thereby improving the management and control of SCD in Nigeria and thereby contribute to our efforts at bringing hope and substantially improve the quality of life of those affected by this disease.

Dr Osagie Ehanire
Honourable Minister
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PREFACE

Sickle cell disease (SCD) is acquired when a person inherits two sickle haemoglobins from both parents (i.e HbSS) or one sickle haemoglobin from one parent and another haemoglobin variant from the other parent (e.g HbSC or HbSβ-thal).

It is estimated that over 300,000 children are born annually with this disease and over 70% of these births occur in Sub-Saharan Africa where majority of the children die before the age of 5 years due to either ignorance or poor standard of care and management.

Nigeria, being the most populous country in Sub-Saharan Africa, has the highest burden of SCD with an annual infant death of about 100,000 which represents 8% of infant mortality in the country. The National Demographic and Health Survey (NDHS) report of 2018 alluded to the fact that at least 1% of children under five in Nigeria are living with SCD.

In recognition of the overwhelming burden caused by SCD as well as the multi-disciplinary and complex nature of the management of this disease, the Federal Ministry of Health, through the Non-Communicable Diseases Control Division decided to bring together a team of experts from different disciplines to develop the first National Guideline for the Control and Management of Sickle Cell Disease.

This evidenced based document is however, due for a review and updating in order for it to continuously meet the expectations and yearning of providing uniformity and standardized procedure in the control and management of the disease in all healthcare facilities across the country.

Hence, it is our earnest desire that this second edition of this very important and strategic document forms the foundation for improving the standard of care for SCD patients in all our healthcare facilities across Nigeria.

Mamuda Mamman
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ACKNOWLEDGEMENT

I sincerely wish to acknowledge and appreciate the team of stakeholders, including my predecessors, who contributed immensely to the development of this document. The excellent team was made up of my team in the Department of Public Health, NCDs Division, line Departments such as Family Health, Hospital Services, Planning, Research and Statistics of the FMOH, Office of the Senior Special Adviser to the President on SDGs, Academia and Research Institutions (NIPRID and NIMR), Professional Bodies and Patients Supports' Group (Nigerian NCD Alliance, Sickle Cell Support Society of Nigeria (SCSSN), Sickle Cell Foundation Nigeria (SCFN), SickleInAfrica consortium), Civil Society Organizations and the organized private sector especially Bond Chemical Industries Ltd, Biomedomics Inc. and Healing Blends to mention but a few.

We sincerely hope that the same spirit of partnership displayed during the development of this document in 2011 and it's review now in 2022 will also be exhibited in the dissemination and utilization of this guideline thereby ensuring effective management and control of SCD in Nigeria.

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LIST OF ACRONYMS

ACS	Acute Chest Syndromes
BP	Blood Pressure
CAT	Computerized Axial Tomography
CS	Caesarean Section
CVA	Cardiovascular Accident
CVS	Chorionic Villous Sampling
DC	Direct Current
DOB	Date of Birth
DIC	Disseminated Intravascular Clotting
EBT	Exchange Blood Transfusion

EDTA	Ethylenediaminetetraacetic Acid
FMOH	Federal Ministry of Health
Hb	Haemoglobin
HbAS	Haemoglobin AS
HbSS	Haemoglobin SS
HbSC	Haemoglobin SC
Hbβ-Thal	Haemoglobin β-Thalasaemia
HDU	High Dependency Unit
HPLC	High Performance Liquid Chromatography
HPFH	Hereditary Persistent Fetal Haemoglobin
HE	Haemoglobin Electrophoresis
HU	Hydroxyurea
IOL	Induction of Labour
IUCD	Intrauterine Contraceptive Device
IUGR	Intra Uterine Growth Retardation
IM	Intramuscular
IV	Intravenous
IEF	Iso-Electric Focusing
LS	Laboratory Standards
MDGs	Millennium Development Goals
MRI	Magnetic Resonance Imaging
MUAC	Mid-Upper Arm Circumference
NCDs	Non-Communicable Diseases
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
NIPRID	National Institute for Pharmaceutical Research and Development

PCR	Polymerase Chain Reaction
PET	Positron Emission Tomography
PGD	Pre-implantation Genetic Diagnosis
PLWSCD	People Living With Sickle Cell Disease
QA	Quality Assurance
SIADH	Syndrome of Inappropriate ADH secretion
SC	Subcutaneous
SCC	Sample Collection Card
SCD	Sickle Cell Disease
SMFE	Systemic Marrow Fat Embolism
USS	Ultrasonography
WHO	World Health Organization

CHAPTER 1

BACKGROUND/INTRODUCTION

1.1 Definition

Sickle cell disease (SCD) is a generic name for a group of inherited haemoglobin disorders characterized by the presence of sickle red cells in the blood which leads to clinical illness (disease). So, literally, sickle cell disease = sickle cell + disease.

SCD is an autosomal recessive disorder, where an affected individual is homozygous for the abnormal HbS gene. This statement to be modified.

1.2 Forms of Sickle Cell Disease

The commonest forms of SCD in our environment in order of prevalence are HbSS, HbSC and HbSβ-thal.

If a person inherited two sickle haemoglobins (HbS) from both parents, the individual has HbSS; while a person inherited one sickle haemoglobin (HbS) from one parent and another haemoglobin variant (HbC) from the other parent has HbSC. Similarly, the individual who inherited one sickle haemoglobin gene from one parent and another abnormal haemoglobin (Hb β-thalassaemia) from another parent has HbSβ-thal.

It is worthy of note that SCD does not include sickle cell trait also known as the carrier state (HbAS)

1.3 The Burden of Sickle Cell Disease

SCD is highly prevalent in sub-Saharan Africa with Nigeria being home to 25–35% of global SCD births[1]. Child mortality from sickle cell disease is presumed to be high but not quantified. This uncertainty contributes to the neglect of sickle cell disease and delays the prioritization of interventions.

Recent data however, from Nigeria's 2018 Demographic and Health Survey (NDHS) showed a prevalence of HbAS (19·7%), HbAC (1·6%), HbSC (0·4%), HbSS (0·9%) of 11, 391 children aged 6–59 months compared to 1·4% for HbSS in a cohort of 3,603 newborns. In addition, the survey reported that 10% of the children aged 6 months to 5 years who were found to have severe anaemia were also shown to have Sickle Cell Anaemia (SCA). Estimates of child mortality from sickle cell disease between 2003 and 2013 with at least 1 younger sibling in the survey had about 370 excess under-5 deaths per 1,000 live births than children with HbAA.

The estimated national average under-5 mortality for children with sickle cell disease between 2003 and 2013 was 490 per 1,000 live births, FOUR times higher than those without sickle cell disease.

[1] Oron, A.P., Chao, D.L., Ezeanolue, E.E. *et al.* Caring for Africa's sickle cell children: will we rise to the challenge? *BMC Med* 18, 92 (2020). https://doi.org/10.1186/s12916-020-01557-2

About 4·2% of national under-5 mortality was attributable to excess mortality from sickle cell disease[2]. Sickle cell disease has received less attention and funding compared to malaria, HIV, TB and vaccine-preventable diseases. The mortality estimate reported from in-depth analysis of the NDHS makes sickle cell disease Nigeria's sixth-largest cause of child death in the GBD, after diarrhoea, malaria, lower respiratory infections, preterm birth, and birth asphyxia.

This will make it difficult for the country to achieve the Sustainable Development Goal target (SDG 3.2) of fewer than 25 under-5 deaths per 1,000 live births by 2030. Evidence-based affordable public health interventions for the management of the disease are available and should be deployed for the prevention and management of SCDs in the country.

The effort to reduce SCD gene pool should be pursued vigorously by the government, NGOs and professional bodies. Sickle cell disease affects nearly 100 million people in the world and it is responsible for over 50% of deaths in those with the most severe form of this disease.

Over 300,000 children are born annually with SCD and over 70% of the births occur in Sub-Saharan Africa where majority of them die before the age of 5 years as a result of poor standard of management.

In Nigeria, sickle cell disease is among the ten (10) priority non-communicable diseases (NCDs) and it contributes significantly to both child and adult morbidity and mortality. By virtue of its population, Nigeria stands out as the most sickle cell endemic country in Africa with an annual infant death of 100,000 representing 8% of infant mortality in the country. It is also estimated that about 24% Nigerian adults have sickle cell trait.

1.4 The Rationale for a National Guideline for the Control and Management of Sickle Cell Disease

The clinical management of patients with sickle cell disease and thalassaemia has become increasingly multi-disciplinary and complex. This trend calls for the development of guidelines for the management of specific clinical problems and protocols for the management of various complications that may be encountered by healthcare workers attending to patients with the disease.

The rationale for the development of this guideline therefore include:

[2] Obiageli E N, Assaf P.O, Alayo S. et al. Child mortality from sickle cell disease in Nigeria: a model-estimated, population-level analysis of data from the 2018 Demographic and Health Survey. VOLUME 8, ISSUE 10, E723-E731, OCTOBER 01, 2021. https://doi.org/10.1016/S2352-3026(21)00216-7

- To optimize and standardize the management and care of sickle cell disease.
- To build a concerted effort to tackle the challenges confronting the control and management of sickle cell disease.
- The clinical management of patients with sickle cell disease and thalassaemia has become increasingly multi-disciplinary and complex. This trend calls for the development of guidelines for the management of specific clinical problems and protocols for various therapeutic procedures and.
- To facilitate uniformity and standardization of care across different disciplines.

Such guidelines and protocols therefore should be regularly revised and updated in line with developments in clinical practice and findings from scientific research.

CHAPTER 2

DIAGNOSIS OF SICKLE CELL DISEASE

Diagnosing Sickle Cell Disease requires adequate history taking, physical examination for the features of SCD and screening for the presence of sickled hemoglobin gene in the blood using a validated Point of Care Screening tool (SickleScan^{R}) for example and confirmation of the positive cases with High Performance Liquid Chromatography (HPLC) or Iso-electric Focusing (IEF) methods.

2.1 Clinical Presentation of Sickle Cell Disease

Patients with Sickle Cell Disease (SCD) have inherited genes that lead to the presence of sickle cells (drepanocytes) in their blood. The clinical features arising from the presence of these sickle cells are protean affecting almost every system of the body and include:

a) Chronic haemoltyic Anaemia;
b) Vaso-occlusive pain episodes;
c) Features of infections;
d) Splenomegaly;
e) Acute chest syndrome;
f) Stroke;
g) Leg ulcers;
h) Priapism;
i) Retinopathy;
j) Pulmonary hypertension;
k) Jaundice;
l) Cardiac dysfunction;
m) Sickle cell nephropathy.

There are also various skeletal abnormalities, such as:

a) Fronto-occipital bossing with striking gnathopathy;
b) Stunted growth;
c) Multifocal osteomyelitis;
d) Long slender extremities;
e) Avascular necrosis of the femoral head;
f) Dactylitis (hand-foot syndrome).

Pain is a defining feature of the disease, with patients experiencing unpredictable recurrent, persistent pain throughout life resulting in frequent hospitalizations although most episodes are managed at home without contact with health care workers. Painful swelling of the hands and feet (dactylitis) can occur as early as six months of age and is often the feature that brings the affected child to medical attention.

The spectrum of clinical expression is heterogeneous, with some people having mild disease while others present with severe complications. It is the presence of these clinical features that will alert one to the presence of the disease and prompt laboratory investigations to confirm the diagnosis.

2.2 Laboratory Diagnosis of Sickle Cell Disease

The laboratory diagnosis of sickle cell disease depends on the demonstration of hemoglobin S (HbS) in patients suspected clinically to have sickle cell disease. The diagnosis can be made in any age group.

Various methods are available for the diagnosis of SCD each of which is dependent on available resources.

Tests showing the presence of sickle haemoglobin are:

- Point of care test): This is now adopted as the first line screening test method for SCD at all levels of healthcare in Nigeria.
- Sickling test
- Solubility test
- Haemoglobin electrophoresis (either in alkaline or acidic pH)
- Blood film
- High-Performance Liquid Chromatography (HPLC)
- Isoelectric Focusing (IEF)
- Other tests include Kleihauer-Betke Test and Molecular Technique

2.2.1 **Point of Care Test (POCT):** This is the first line of screening for SCD with a validated Point of Care Test tool such as **SickleScan^{R}**. It is a form of testing in which the analysis is performed where healthcare service is provided close to or near the patient. POCTs are inexpensive, reliable, require only a pin prick of blood, and show high specificity and sensitivity in the determination of the different haemoglobin phenotypes in the presence of the high HbF levels in newborns.

Principle of Point of Care Test is a lateral flow chromographic qualitative immunoassay for the rapid determination of the presence of HbA, HbS and HbC.

Procedure of Point of Care Screening for SCD

Procedure for testing should be according to the manufacturers' specification

Advantages

1. Fastest testing results
2. No specialized training is required
3. No electricity required
4. Very reliable and efficient for Newborn screening. Screening
5. Test could be done anywhere

Disadvantages

1. Gives only qualitative results

NB: Considering the advantages of this point of care, the sickling test and solubility test described below

are now less frequently used and discouraged since they are less reliable.

2.2.2 Sickling Test

This test can be performed in the laboratory of a primary health care center.

Principle: This shows the changes in shape that is undergone by HbS containing red cells when they are deprived of oxygen by sealing the slide on which the blood sample is placed, with paraffin wax.

Materials: *Light microscope, Glass slides, Microscope glass cover slips, Soft paraffin wax, Petroleum jelly, Sterile lancets, Sterile syringe and needle, EDTA bottle.*

Procedure:

a) Collect 2mls of venous blood by sterile procedure (An alternative is to obtain sample by lancet finger capillary prick)

b) Place the sample into an EDTA bottle and mix gently

c) Place a drop of the blood on a clean grease-free slide

*d) Place a clean cover slip on the blood (**Note**: Ensure that the margins of the slide are beyond those of the sample)*

e) Examine the sample to confirm the initial shape of the red cells

f) Place paraffin wax on the edges of the cover slip to adequately seal off oxygen

g) Allow to stand for one hour before examining the blood film.

Note: *HbS containing red cells undergo a change in shape making them look like crescents, sickles or dried holly leaves.*

Interpretation of Sickling Test:

A positive test shows that person has sickle haemoglobin but cannot distinguish HbAS, HbSS and HbSC. It therefore requires an unrelated second line method for confirmation of result.

Advantages of Sickling Test:

a) Can be carried out in a low resource setting
b) Easy to conduct and does not require intensive training.

Limitations of Sickling Test:

a) Not used in screening newborns
b) Could miss other hemoglobinopathies

2.2.3 Solubility Test

This test can be performed in the laboratory of a primary health care centre.

Principle: When a sample of haemoglobin S containing blood is added to a sample of either a buffered solution of sodium metabisulphite or sodium dithionite (these are reducing agents), a precipitate forms in the tube as a result of the reduction of the Hb S. **Note:** *When HbS is exposed to conditions of reduced oxygen tension, it undergoes configuration changes and forms a precipitate.*

Materials:

a) Anhydrous potassium dihydrogen phosphate 33.78g
b) Anhydrous potassium hydrogen phosphate 59.33g
c) White saponin 2.5g
d) Distilled water 250ml
e) This is stored at 4^{o}C
f) Working Solution: Prepared by adding 100mg of sodium metabisulphite to 10mls of stock buffer
g) Sodium metabisulphite (100mg)
h) Stock buffer (10ml)

Procedure:

a) Place 1drop of blood in a tube containing 1ml of the working solution
b) Centrifuge the mixture at a speed of 3000 r.p.m. for five minutes
c) Examine the contents of the tube
d) Compare with similarly prepared known Hb-AA and Hb-AS controls. This shows a heavy haemoglobin precipitate (in the HbS containing sample) on the surface, below which is a pink mauve coloured solution.

Interpretation of solubility Test:
Positive result suggests the presence of sickled haemoglobin and is semi-quantitative.

Advantages of Solubility Test:

a) Can be carried out in a low resource setting
b) Easy to conduct and does not require intensive training.

Limitations of Solubility Test:

a) Not used in screening newborns
b) Could miss other hemoglobinopathies
c) It requires an unrelated second line method for confirmation of result.

2.2.4 Haemoglobin Electrophoresis (HE)

Haemoglobin electrophoresis can be performed in many general hospitals (Secondary health care facilities).

Principle: This method depends on the migration of haemoglobin in an electrical medium. coincide with that of HbE and HbO in alkaline in an acidic medium. In Nigeria, Hb electrophoresis in an alkaline medium is more commonly performed. Therefore, for the confirmatory diagnosis of SCD a combination of Hb electrophoresis with outcome of the POCT test should be adopted especially where HPLC and IEF are not available/accessible.

Cellulose Acetate Electrophoresis

Materials:

a) Electrophoresis chamber
b) DC Power pack
c) Multi-applicator plate
d) Multi-applicator
e) Cellulose acetate strips
f) Filter paper
g) 2 Kidney dishes
h) Pasteur pipettes (long type).

Procedure:

a) Preparation of electrophoresis chamber and cellulose acetate strips

- Two pieces of filter paper are fixed across each shoulder and into each outer compartment of the electrophoresis chamber

- 100mls of tris-EDTA-borate (TEB) buffer is poured into each outer compartment and 50mls into each new compartment of the chamber
- 50mls of TEB is poured into a large kidney dish
- A cellulose acetate strip is immersed and left in the buffer in the kidney dish for 10 minutes.

b) Preparation of haemolysate:

- 0.5ml of potassium cyanide – EDTA working solution is pipetted into each tube of a row of 16 tubes
- Using a Pasteur pipette, one drop of anticoagulated blood is added to the working solution
- The contents of each tube are mixed by vigorous but gentle tapping of the base of the tube to lyse the red cells.

c) Application of haemolysates to a shandon multi applicator plate:

- Using samples of known Hb AA and Hb AS blood as controls placed at the extreme segments of the multi-applicator plate, one drop of each sample is placed on each segment of the multi-applicator with a long Pasteur pipette
- Blunt forceps are used to remove the wet cellulose acetate strip from the kidney dish in which it had been immersed in buffer. Excess buffer is removed by blotting the strip between two pieces of filter paper
- With the cellulose acetate paper laid on a smooth piece of cardboard, the teeth of the multi-applicator are applied to the haemolysates on the respective segments of the multi-applicator plate
- The teeth of the multi-applicator are placed on the buffer impregnated cellulose acetate strip along a line 1.5cm from one of the lateral margins of the strip.

d) Electrophoretic "run":

- Excess buffer is removed from parts of the filter paper lying on the shoulders of the electrophoresis chamber using tissue paper.
- The haemolysate containing cellulose acetate strip is fixed on both shoulders of the chamber so that all samples are parallel to the shoulders. Shoulder supports to hold the strip in position.
- After having made the electrical connections, the chamber is covered, and the DC power pack is switched on, electrophoresis is carried out from cathode to anode at 250 volts (5 to 10m A) for 30 minutes.

e) Staining:

- Ponceau-S stain is used to stain the cellulose acetate strip, which had undergone an electrophoresis „run" for 10 minutes.

- Excess fluid is blotted off using filter paper
- The strip is dried face downwards
- All samples that show the migration of the haemoglobin to the HbSS position are subjected to the solubility test to exclude other haemoglobin types that may migrate to similar positions under the same conditions
- Haemoglobin-S will give a positive solubility test, while other haemoglobin types will give a negative solubility test.

Advantages of Hemoglobin Electrophoresis:

a) More specific in diagnosing Sickle Cell and related disorders
b) Simple and rapid.

Limitations of Haemoglobin Electrophoresis:

a) Requires electricity
b) Could produce false results.
c) It requires an unrelated second-line method for confirmation of result.

2.2.5 Blood Film

This plays a dual role in demonstrating sickle cells and features of complications of sickle cell disorder such as, megaloblastic anemia, iron deficiency (though rare), bacterial infection, or the presence of parasites like malaria.

Principle: The nucleus and cytoplasm of blood cells when exposed to Hemotoxylin- Eosin based stain like Leishman stain differently.

Materials:

a) 1 clean glass slide
b) 1 glass spreader
c) 1 capillary tube
d) Leishman stain (preparation, see Appendix)
e) 1 Binocular optical microscope
f) Immersion oil.

Procedure (Blood Film Preparation):

a) A drop of anticoagulated blood is placed on a clean glass slide about 1–2cm from one end with a capillary tube
b) A second glass slide (spreader) is placed at an angle of 45^{o} to the horizontal and moved quickly as it makes contact with the drop of blood.
c) The film is air-dried and then flooded with Leishman stain for 2 minutes after which buffered distilled water double the volume of the stain is added for 5 – 7 minutes (differentiation)
d) The film is then washed with water till it acquires a pinkish tinge

e) The back of the slide is wiped before drying in upright position
f) The film is examined under the microscope. In SCD, you may find the following (i) Sickle Cells, (ii) Target Cells, (iii) Polychromatic Cells, and; (iv) Malaria parasites.

Advantages of Blood Film:

a) Simple and cheap
b) Can detect co-morbidity e.g malaria parasite etc.
c) It is rapid.

Limitation of Blood Film:

It Requires a higher ~~level~~ level of manpower.

2.2.6 High-Performance Liquid Chromatography (HPLC)

Principle:

a) Readily separates proteins that cannot be resolved by other means
b) Allows for accurate quantification of normal and variant hemoglobins even at low concentrations, enabling differentiation of Hb Sβ^+ thalassemia from sickle cell trait (Hb AS) as well as identification of compound heterozygous disorders such as Hb S-HPFH (hereditary persistence of fetal hemoglobin) and Hb S-thalassaemia.

Procedure:

The equipment is complex and fully automated

a) Samples can be obtained from heel prick on a filter paper for newborns and infants (dried blood spot)
b) For some equipment variants, liquid blood samples are used.

Advantages of HPLC:

a) It saves time
b) Requires less staff
c) Can handle large samples at the same time
d) Requires very small sample volume
e) Results could be qualitative and quantitative
f) Process is automated with high precision
g) Enables early detection in newborns.

Limitations of HPLC:

a) Very expensive (equipment, maintenance, and testing)
b) Requires electricity
c) Requires optimal room temperature to function accurately
d) It separates glycosylated and other derivative forms of hemoglobin which can make interpretation difficult
e) It requires an unrelated second-line method for confirmation of result.

2.2.7 Isoelectric Focusing (IEF)

IEF is a method of separating proteins according to their isoelectric points in a P^H gradient.

Principle: Capillary isoelectric focusing technology allows for the separation of very small samples, quantification, and automation of sampling.

Advantages of IEF:

a) Capable of much higher resolution than hemoglobin electrophoresis
b) It gives good separation of HbF and HbA
c) Can be semi-automated
d) Runs a large number of samples
e) Suitable for screening newborn

Limitations of IEF:

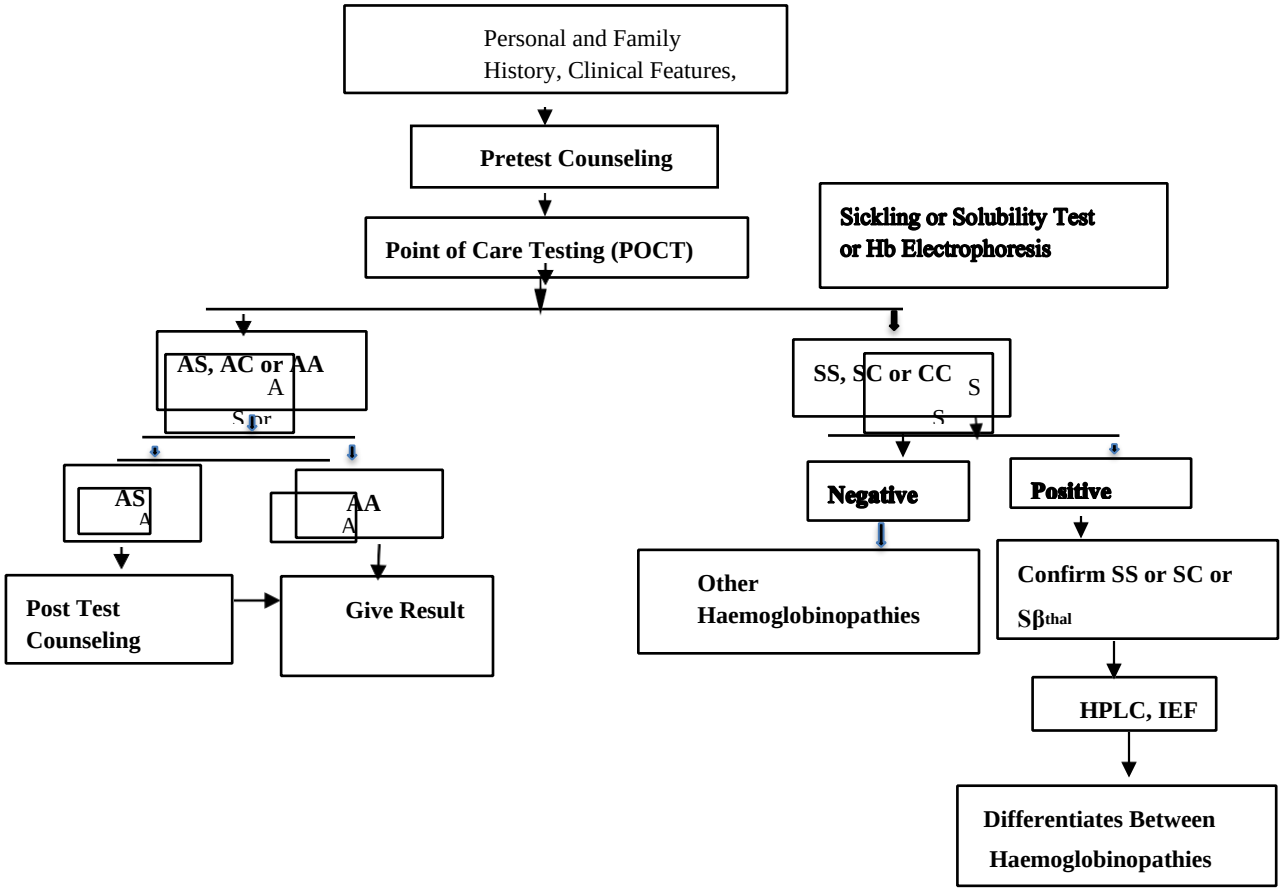
a) Very expensive (equipment, maintenance, and testing)
b) Requires electricity
c) Requires optimal room temperature to function accurately
d) It separates glycosylated and other derivative forms of hemoglobin which can make interpretation difficult.
e) It requires an unrelated second-line method for confirmation of result

2.2.8 Other Tests

a) **Molecular Technique** (mutation detection and sequencing analysis): Used predominantly for prenatal diagnosis.
b) Preimplantation Genetic Diagnosis: is used to analyze embryos genetically before their transfer into the uterus.
c) Pre-natal Diagnosis: Prenatal diagnostic testing involves testing the fetus before birth (prenatally) to determine whether the fetus has sickle cell disease.
d) **Kleihauer-Betke test**: This acid-elution test detects the presence of cells with a high fetal hemoglobin content and can be used to characterize co-existent HPFH with sickle cell disease.

Note: ***In our setting, any diagnosis of SCD should include at least two tests, which must be unrelated in methods***.

Figure 1: Algorithm for the Screening and Definitive Laboratory Diagnosis of Sickle Cell Disease



Note: 1. *This applies at all levels of care except in tertiary healthcare facilities where Hb electrophoresis testing may still be feasible.*

2. *With the advent of rapid point of care testing (POCT) when screening is positive the next level of testing should be HPLC or IEF for confirmation.*

2.3 Quality Assurance and Laboratory Standards

This is a set of procedures intended to ensure work meets specified requirements. Components of a good Quality Assurance (QA) and Laboratory Standards (LS) Include:

- Quality Control
- Quality Assessment

2.3.1 Quality Control

This is a set of procedures that ensure adherence to defined quality criteria. Standard Operating Procedures must be written out, displayed, and strictly adhered to. Quality control is an internal exercise and a quality control officer should be designated.

2.3.2 Quality Assessment of a Laboratory

This is a system for evaluating the performance of its service delivery. This is usually done by external assessors e.g. professional regulatory bodies and state ministries of health.

Note:

- *Training and re-training of personnel in haemoglobinometry is an essential component of a good quality assurance programme*
- *Laboratory equipment and reagents must meet set international standards*
- *Reference laboratories must be involved in an external quality assurance evaluation.*

CHAPTER 3

MANAGEMENT OF ACUTE COMPLICATIONS IN SICKLE CELL DISEASE

3.1 Introduction

The clinical features of SCD, some of which are life threatening, can be markedly variable among individuals, depending also on the form of the disease (HbSS, HbSC or HbSβ-thal). The acute complications, can occur unpredictably, usually without clear precipitating factors. More than 90% of hospital admission occur because of the acute episode of SCD. This section of the guideline is focused on the management of acute complications of SCD.

Goal of Management of SCD: The overall goal of management is to improve quality of life and life expectancy of the affected individuals.

Objectives of Clinical Management of SCD:

a) Maintain a steady state of health
b) Prevent and reduce the number of crises and complications
c) Treat crises and complications promptly and effectively
d) Promote a healthy lifestyle and a positive self-image.

3.2 Acute Clinical Presentations

Acute clinical presentations in SCD include the following:

- Sickle Cell Crisis
    a. Painful crises (Vaso-Oclusive Crises)
    b. Acute Anaemia
        i. Sequestration crises/Acute splenic sequestration (ASS)
        ii. Aplastic crises /Transient red cell aplasia (TRCA)
        iii. Hyper-haemolytic syndrome (HHS)

- Priapism
- Acute Chest Syndrome
- Stroke
- Acute Sepsis Syndrome
- Acute Febrile Illness and other signs of infection
- Acute Hepatobiliary Complications
- Acute Ocular Complication
- Acute Renal Failure
- Acute Osteomyelitis and Septic Arthritis
- Acute Multisystem Failure

3.2.1 Sickle Cell Crisis:

This refers to a worsening, over a short period, of the symptoms and signs of SCD; usually associated with pain and/or shortage of blood (anaemia).

Comprehensive management of the patient in crisis has two aspects namely:

a) Treatment of acute clinical problems during the episode of crisis; and
b) Arrangements to ensure continued care of the person in (post-crisis) steady state.

Note:

- ***Steady state is the interval between crises when the individual is in relative good health.***

- ***Although, increased haemolysis associated with sickle cell crises can be caused by several coexisting conditions such as infection (e.g. bacterial, viral and parasitic especially malaria) and blood transfusion reactions, it is currently not considered that 'haemolytic crisis' is a unique entity.***

Predisposing Factors for Sickle Cell Crisis:

a) Exposure to cold / drenched by rain
b) Physical exertion

c) Dehydration
d) Injury (including surgical injury)
e) Psychological stress
f) Idiosyncratic (peculiar to the individual)
g) Idiopathic (unidentified)
h) Infections/infestations
i) Some drugs.

Initial Evaluation of a SCD Patient in Crisis should include:

a) History of pain, self-assessment of pain, and prior treatment taken before arrival at hospital
b) History of usually effective analgesics
c) History of drug allergies
d) Assessment of vital signs: blood pressure, heart rate, respiratory rate, oxygen saturation (administer oxygen if O_2 saturation <90%) and temperature.
e) History of increasing jaundice and passage of coke-coloured urine
f) Assessment of areas of bone tenderness.

Table 1: Initial Treatment of Patient in Sickle Cell Crisis

Pain relief (preferably in a comfortable and quiet environment)
Optimal hydration
Identification and treatment of infections and/or other cor-morbid conditions
Blood transfusion *if necessary*
Address specific clinical problems *e.g. stroke, acute chest syndrome, priapism.*

Table 2: Investigations That Influence Immediate Management of Sickle Cell Crisis

Urgent Hb/PCV, WBC**, Platelet and Reticulocyte counts, ESR
Examination of Blood Film especially for malaria parasites.
Plasma Bilirubin Level (total & conjugated)
Serum Urea, Electrolytes, Creatinine & C-Reactive Protein (CRP)
Infection Screening (blood, urine, stool, sputum etc) as necessary
Abdominopelvic ultrasound scan as necessary
Chest X-Ray

Pulse Oximetry (Arterial Blood Gases if SaO_2 <92%)*
Transcranial Doppler Ultrasonography (TCD USS)
Computerized Axial Tomography (CAT)
MRI/PET

**** Low blood oxygen is* NOT *common in sickle cell crises***

*****corrected for nucleated RBCs.***

Note:

- ***Although a rise in the plasma level of acute phase reactants (e.g. C-reactive protein) may indicate the transition from steady-state to crisis, the diagnosis of crisis is made on clinical grounds***
- ***The frequency of crisis varies from person to person and from time to time in the same person*.**

Types of Sickle Cell Crises:

a) **Painful (vaso-occlusive) crisis:** caused by obstruction of blood vessels in different parts of the body

b) Acute Anaemia:

i) Sequestration crises/Acute splenic sequestration (ASS) : results from trapping of red blood cells in the spleen or liver

ii) Aplastic crises /Transient red cell aplasia (TRCA) : Acute reduction of red cell production in the marrow caused by parvovirus B19.

iii) Hyper-haemolytic syndrome (HHS)

Aplastic crisis:

a) Painful (Vaso-Occlusive) Crisis

This is the type of crisis caused by obstruction of blood vessels, which leads to tissue ischaemia /infarction and pain. So, the main feature is pain of sudden onset, with or without history of a predisposing factor. The bones are most frequently involved, and they become mildly to extremely painful and may also become swollen or tender, or both.

The patient needs rapid pain relief before full medical assessment. This approach enhances patient co-operation and confidence in the carer. It is the most frequent type of sickle cell crisis.

Note: ***If the clinical impression of crisis is made following initial brief (about 5 minute) of clinical evaluation, and the patient is in pain, give analgesics and allow an appropriate interval for pain to subside before full assessment and further treatment.***

Table 3: Fluid Management in Painful Crisis

Adults	Children
1.5 L/m^2/day OR 3L/day	100 – 120 ml/kg/day (can be given orally if there is no vomiting or if patient can drink that volume

Note: ***SCD impairs renal function and, to reduce the sodium load, 5% dextrose in water or dextrose saline is preferred. It is also important to avoid hypertonic fluid such as 10% dextrose.***

Table 4: *Blood Transfusion in Painful Crisis

Type of Blood	Amount Required	
	Adult	**Children**
Red Cell Concentrates	To steady State	10 ml/kg
Sedimented Cells	To steady State	15 ml/kg
Whole Blood	To steady State	20 ml/kg

***Transfuse blood if Hb < 6g/dl, or > 2g/dl below steady-state value, or there are acute features of severe anaemia.**

Note: *If the patient has features of infection, such as fever, send relevant samples for microbiology before starting broad-spectrum antibiotics, and anti-malarials in malaria endemic regions.*

Table 5: Treatment of Acute Pain in Sickle Cell Disease

Degree of Pain	Opioid Naive	Opioid Tolerant
Mild	**Adult:** ● Dihydrocodene tablets 30 mg 4 hrly plus ● Paracetamol 1g 4 hrly	Immediate-release oral formulation of stronger opiate e.g. morphine 4 hrly
	Children: ● Paracetamol 20mg/kg 4 to 6hrly with/without Ibuprufen 10mg/kg 8hrly Or diclofenac 1mg/kg 8hrly ● Dihydrocodene 1mg/kg 8hrly	

Moderate/Severe	**Adult:** ● Diamorphine 2.5-5mg/4hrly s.c. Or morphine 5 – 10mg stat or pentazocine 15 mg 8-hrly. ● **Inj diclofenac 75mg 1-2 hrly after opioids ● **Inj tramadol 100mg 1-2 hrly after NSAIDs	● Injection of opiate diamorphine 10-20mg/2-4 hrly s.c. ● Injection of opiate e.g. pentazocine 30 - 60 mg 8-hrly

Degree of Pain	Opioid Naive	Opioid Tolerant
	Children: ● Oral morphine 0.4mg/kg or diamorphine 0.1mg/kg in IV infusion or IM/SC stat to immediate pain relief. ● **Then maintenance:** Slow-release morphine 1mg/kg (rounded up to 5mg) every 12 hrs with oral morphine 0.3mg/kg every 3hrs as necessary. ● Or oral morphine 0.4mg/kg ● Or pentazocine at appropriate doses ● ****Inj diclofenac 1mg/kg after opoids** ● ****Inj tramadol 100mg 1-2 hrs after NSAIDs**	

*****This is necessary to reduce the frequency of the patient's need for opioids; as well as to prevent the patient from returning to base-line intensity of pain in-between the doses of opioids.***

Note:

- *Assess pain relief every 15-30 minutes if patient is awake and while he/she is left in a comfortable place*
- *Give anti-emetics if indicated: procholorperazine 250 µg/kg t.d.s. or cyclizine 12.5- 25 mg t.d.s.*
- *Monitor pain, sedation, vital signs, respiratory rate, oxygen saturations: every 30 min until pain is controlled and patient is stable; then every 2 hours*
- *If respiratory rate less than 10/min, omit the next dose of opioids and give 10 µg/kg Naloxone IV, followed by 100 µg/kg*
- *Discharge patient when pain is improving or controlled with reduced dose of oral analgesia e.g tramadol and NSAIDs*
- *Arrange for home and outpatient follow-up appointment as applicable.*

Acute Surgical Abdomen Vs Painful Abdominal Crises:

It could be difficult to distinguish between these two conditions, especially if patient has abdominal distension and pain; which can occur in both. When this uncertainty occurs, refer to a centre where surgeons can review and if clinical state worsens despite conservative management, surgical intervention may be justified

Note: The two conditions may co-exist in the same patient.

Hand – Foot Syndrome:

Bone pain with inflammatory swelling of the dorsum of the hands and feet is an early manifestation of sickle cell disease seen particularly in children.

The distal bones, such as those of the hands and feet, are usually affected in infancy and early childhood up to the age of about 4 years.

It is pathognomonic of SCD and its occurrence should prompt laboratory investigations to confirm the diagnosis. The distal bones, such as those of the hands and feet, are usually affected in infancy and early childhood up to the age of about 4 years.

It may rarely occur in adolescents and adults. It is a unique form of painful (vaso- occlusive) crises and its management principles are similar (see tables 4 and 5).

Although this is a sterile bone manifestation, secondary bacterial infections may occur; therefore, necessitating the use of broad-spectrum antibiotic such amoxicillin-clavulanic acid 50mg/kg/day in 2 divided doses.

c) Acute Anaemia

i) Sequestration Crisis/ Acute splenic sequestration (ASS)

This is pooling (sequestration) of a large proportion of blood in the spleen or in the liver. Usually occurs in children < 6 years and some HbSC or HbSβ-thal adults; unusual in HbSS adults. It is a major cause of death in children with SCD aged 0-2 years.

Features of sequestration crisis include:

a) Marked pallor
b) Precipitous fall in Hb Level
c) Sudden, progressive enlargement of the spleen, may be associated with increase in abdominal girth
d) „Hypovolemic" shock due to pooling of blood in spleen and reduced circulating volume
e) Reticulocytosis and/or nucleated red cells in the blood film. This helps to differentiate sequestration from aplastic crisis.

Treatment of Sequestration Crisis:

a) Rapid transfusion of whole blood or red cell concentrate. Type and crossmatch RBC and transfuse carefully in small aliquots – starting with number of ml/kg of red cells equal to Hb number of grams/dL. E.g., for patient with Hb 3g/dL, give 3 ml/kg of packed RBC as initial transfusion; wait

3-4 hours for equilibration and give subsequent small volume transfusions as needed. Do not aim for baseline or normal Hb level in initial transfusions or Hb level > 10g/dL, if baseline Hb is not known, to reduce the risk of hyperviscosity and stroke. The sequestered red cells can reenter circulation hours or days after RBC transfusion and may increase the risk of hypervolemic shock, acute cardiac failure, hypertension and stroke.

b) The post-transfusion Hb level may be higher than the expected 1g/dl per unit of blood transfused; because the sequestered or pooled red cells re-enter the circulation. In view of this the amount of blood required would be 10ml/kg for red cell concentrate or 15ml/kg for whole blood. Alternatively, emergency exchange blood transfusion (EBT) may be done, if feasible in the circumstances

c) Teaching parents, school teachers and care givers how to palpate for an enlarged spleen or liver helps early detection of sequestration crisis and reduces the mortality rate.

d) Monitor spleen size for recurrence

Prevention of Sequestration Crisis:

This is advised after 2 episodes, using one of 2 approaches:

a) Elective splenectomy is indicated after two episodes of sequestration crises occurring in less than six months apart

b) Hypertransfusion or EBT in malaria endemic regions.

N:B Give penicillin prophylaxis post splenectomy

ii. Aplastic Crisis/Transient Red Cell Aplasia

This refers to an acute form of acquired red cell aplasia secondary to infection by parvovirus B19, a DNA virus that replicates inside immature red blood cells in the bone marrow, resulting in severe anaemia and low reticulocyte count. It is rarely recurrent.

Features of aplastic crisis include:

a) Weakness and easy tiredness

b) Headaches

c) Fever

d) Facial erythema

e) Low Hb/gradual fall in Hb (usually in children)

f) Reticulocyte count < 2% (of total red cell count)

g) Leucocyte and platelet counts may be reduced

h) Serum IgM antibody to parvovirus B19 virus in blood

Treatment of Aplastic Crisis:

a) Isolate patient, especially from expectant mothers to reduce the risk of fetal Parvovirus B19 infection

b) Transfuse blood with a target to achieve the patient's steady state Hb level.

c) Intravenous immunoglobulin should be given to immune deficient patients.

Prophylaxis:

Parvovirus B19 infection can be prevented by vaccination of non-immune individuals who have sickle cell

disease, or other chronic haemolytic anaemias.

iii) Hyperhaemolytic Syndrome (HHS)

HHS is a medical emergency characterized by acute exaggeration of RBC destruction and reticulocytopenia which occurs following multiple blood transfusion because of alloimmunization. There is autologous and allogenic RBC destruction. It also tends to reoccur in the same patient following subsequent blood transfusion. These indicated an immunological or genetic predisposition due to secondary immune response.

Predisposing Factor:

- Multiple blood transfusion
- Disparity in blood group
- Infections

Clinical and Laboratory Features:

- Progressively decreasing PCV despite blood transfusion
- Hemolysis
- Reticulocytopenia
- Alloantibodies

Investigation:

- CBC, LFTs, Reticulocyte count, Blood group, Coombs Test, Serial PCV

Management:

- Mainly supportive
- RBC (Blood transfusion) if necessary
- Immunosuppressive agent/steroids (Oral Prednisone, Rituximab, Ecolizumab)
- Erythropoietin Stimulating agent.

3.2.2 Acute Sepsis Syndrome

Sickle Cell Diseases patients are prone to acute sepsis particularly due to auto splenectomy in adults. They are susceptible, formerly to encapsulated organisms (S. pneumonia, H. influenza and Neisseria Meningitidis) for those with early signs of sepsis especially Fever >38^{o}C.

It requires aggressive treatment:

Management:

i. CBC
ii. Vital signs should be closely monitored
iii. Liver function test

iv. Renal function test
v. Septic work up (urine, blood stool, CSF and sputum culture)
vi. Commenced 3rd generation cephalosporins initially
vii. Macrolides in case of respiration symptoms
viii. Commence Carbazepam group of Antibiotics (Emiphenem or Meranphenem) if other above medications failed.
ix. **Hourly observations** for first 6-12 hours – pulse, respiratory rate, SaO2 (PAO2), temperature, Glasgow Coma Score
x. **Be alert for complications** e.g. Acute chest syndrome, stroke

3.2.3 Acute Febrile Illness and other signs of infection:

Investigation:

- Full blood count, blood cultures, and malaria test.
- Urinalysis (dipstick), urine microscopy, and urine culture/sensitivity,
- Group and crossmatch,
- Creatinine, urea, electrolytes,
- Chest x-ray if any respiratory symptoms/signs,
- Bone imaging +/- orthopedic review +/- joint aspiration if any limb symptoms,
- If signs of meningeal irritation or child <18 months with unexplained fever, consider lumbar puncture

iii Insert IV cannula
iv IV FLUIDS – Hydrate, as per hydration guideline
v Start appropriate antibiotics, broad spectrum, as per local guideline for specific infection or septicemia

Consider: malaria treatment, oxygen, pain relief, transfusion if indicated

3.2.4 Priapism

This refers to a prolonged painful, purposeless, penile erection, not associated with sexual stim**ulation.**

Types of Priapism:

a) Stuttering, lasts < 4 hr; resolves spontaneously
b) Major or fulminant, with duration of > 4 hrs. ; less frequent.

Onset:

Mostly in the early hours of the morning and at nights.

Predisposing Factors:

a) Full bladder, in the night,
b) Dehydration
c) Sexual activities
d) Fever
e) intake of fluids in the night usually after 10pm
f) Diuretics in the night

Complications:

a) Erectile dysfunction
b) Impotence
c) Psychosocial problems.

During clinical assessment of a person with priapism, it is important to ascertain if there is urinary retention and whether the glans penis is soft or turgid. This influences treatment. If the patient is able to pass urine and the glans is soft, then the corpus spongiosum is probably NOT affected, and a glans-cavernosa shunt may confer clinical benefit.

By contrast, if the patient is unable to pass urine or the glans is turgid, the corpus spongiosum is probably affected and a glans-cavernosa shunt is unlikely to be effective in draining blood from the corpora cavernosa. In such individuals, a surgical shut between the dorsal vein of the penis and the corpora cavernosa may be more beneficial.

Management of Stuttering (Minor) Priapism:

a) Encourage patient to empty bladder before going to bed
b) Avoid diuretics and those things that cause diuresis
c) Tab Stilboesterol
d) Hydrate the patients
e) Analgesia
f) Muscle relaxants
g) Alkalization of urine
h) Give Alpha-Agonist such as slow release tablets of etilefrine. The effect lasts for 8-9 hrs. Start with 25mg daily taken by 10-11 pm. If clinical response is unsatisfactory after 2 weeks, increase

the dose to 50mg daily. If response still not satisfactory, increase the dose by 25 mg every 2 weeks up to a maximum dose of 100mg

i) If the total daily dose of etilefrine is greater than 50mg, it is recommended that 50mg be taken by 10-11 pm, and the rest by 4-5 pm

j) Monitor BP and erectile function in people on etilefrine, because it is a vaso- constrictor.

Note: ***If tablet etilefrine is not effective in preventing priapism, cyproterone is added to the regimen. This anti-androgen is preferred to the oestrogen, stilboesterol, which has feminizing effects such as breast enlargement (gynaecomastia).***

Management of Major Priapism in Sickle Cell Disease:

a) Give pain killers to comfort the patient

b) Give fluids (oral or intravenous)

c) Exchange blood transfusion

d) Urosurgeons should aspirate and irrigate corpora cavernosa with 6-10 mg of injectable etilefrine diluted in 20mls of saline. If there is no response (detumescence) after 1 hour, repeat irrigation with etilefrine. Phenylephrine may be used in place of etilefrine, but is less effective

e) If repeat irrigation of cavernosa with etilefrine does not lead to detumescence after 1hour, the urosurgeons should create shunts between the corpus spongiosum and corpora cavernosa to drain deoxygenated and sickled blood sequestered in the cavernosa into the spongiosum, and from there to the general circulation.

Note: Possibly because the transfused blood does not sufficiently enter the penile sinusoids, exchange blood transfusion is usually not effective as treatment of established episodes of fulminant priapism, the management of which may not give satisfactory results.

3.3.3 Acute Hepatobiliary Complications

1. Acute hepatic sequestration:

- **Evaluation:** Obtain FBC and LFT, and rule out other causes of rapid fall in Hb
- **Treatment:** Treat as severe acute anemia; perform simple or exchange blood transfusion, as needed

3. Hepatic crisis:

- **Evaluation:** Obtain FBC, LFT, PT/PTT, and abdominal US/MRI
- **Treatment:** Treat symptomatically; monitor closely for potential deterioration

4. Intrahepatic Cholestasis:

- **Evaluation:** Obtain FBC, LFT, Abdominal US/MRI
- **Treatment:** Admit and monitor closely
- Perform exchange blood transfusion

5. Choledocholithiasis:

- **Evaluation**: Obtain FBC, LFT, Abdominal US/MRI, Endoscopic retrograde cholangiopancreatography (ERCP).
- **Treatment:** Consult surgeons.

3.3.4 Acute Chest Syndrome (ACS).

Acute chest syndrome (ACS) is an acute pulmonary illness and an important cause of death in SCD. It is recognized by a new opacity in a chest x-ray, usually with acute signs and/or symptoms; such as fever, cough, wheeze, breathlessness or chest pain.

Causes include:

a) Chest infection

b) Embolism of bone marrow fat to the lung; the embolus obstructs blood vessels and this causes infarction of lung tissue

c) Sequestration of erythrocytes in pulmonary blood vessels; this also causes vaso- occlusion and lung infarction.

Note:

- *To reduce the risk of mortality, especially in adults, all three causes are assumed to be present and treatment is given accordingly*
- *Infection is a more common cause of ACS in children compared with adults; infarction and bone marrow fat embolism are more common in adults relative to children. Repeated episodes of ACS are associated with chronic sickle lung disease.*

Table 6: Clinical Features of Acute Chest Syndrome

Symptoms	**Signs**
Fever	Breathlessness
Cough	Wheezing
Chest pain	Nasal flaring
Haemoptysis (though rare)	Tachypnoea
	Tachycardia
	Normal chest findings
	Dullness to chest percussion

Symptoms	Signs
	Crepitations in lungs
	Hypoxia

Note:

- *Initial chest x-rays may not show new opacities in the lungs, serial radiographs are required in such situations*
- *The enzyme secretory Phospholipase A_2 ($sPLA_2$) is increased before the clinical features of ACS become obvious, and is a laboratory predictor of this condition*
- *Plasma level of C-reactive protein (CRP) correlates very well with that of secretory phospholipase A_2 and in ACS serum CRP is usually $\geq$5mg/L*
- *It is important to distinguish between Acute Chest Syndrome from vaso-occlusive crisis involving the bones of the chest for which the treatment is different.*

Treatment:

a) Admit to hospital
b) Oxygen is beneficial if there is hypoxaemia; may not if blood oxygen saturation is normal
c) Exchange Blood transfusion (EBT), but if not possible, do a top-up so as to facilitate oxygen delivery to the tissues
d) Broad-spectrum antimicrobials, including clarithromycin for mycoplasma and Chlamydia
e) Bronchodilators, such as nebulized salbutamol to improve oxygen delivery to the Lungs
f) Anticoagulant therapy, especially if marrow fat or thromboembolism is suspected
g) Analgesics, to reduce chest pain which may inhibit breathing and impair oxygenation
h) Cautiously maintain optimal hydration (to prevent lung oedema). -

Prevention:

Hydroxyurea therapy or hypertransfusion should be commenced after recovery to prevent recurrence.

3.3.5 Acute Ocular Complications:

- Immediately examine for hyphema anyone with SCD who presents with eye trauma. If hyphema is present, immediately refer to an ophthalmologist for further management.
- Promptly refer anyone with SCD exhibiting signs and symptoms such as protrusion of the eye, changes in visual acuity (flashers or floaters), and unilateral or bilateral loss of vision to an ophthalmologist capable of performing a dilated eye exam to assess visual acuity, intraocular pressure, and the peripheral retina.

- Manage acute ocular complications in consultation with an ophthalmologist, hematologist, and other specialists with expertise in SCD.

3.3.6 Acute Renal Failure

i. In the setting of an acute rise in serum creatinine of ≥ 0.3 mg/dL, (265 μmol/L) - Monitor renal function daily, including serum creatinine and fluid intake/output
ii. Avoid potential nephrotoxic drugs and imaging agents
iii. Evaluate the person thoroughly for all potential etiologies in consultation with a nephrologist as needed
iv. Do not give blood transfusions to treat ARF unless there are other indications for transfusion
v. Use renal replacement therapy (e.g., hemodialysis) when needed for acute renal failure

3.3.7 Acute Osteomyelitis and septic arthritis

i. **Investigations:** Blood culture, direct bone aspirate or joint aspirate, Ultrasound, X-Ray, MRI/PET
ii. Start with an initial broad-spectrum intravenous antibiotics awaiting the culture results for between 5-7days.
iii. Continue with oral antibiotics for the recommended minimum of 6 weeks
iv. In absence of cultures, use antibiotics with good salmonella and Staph. aureus coverage
v. Obtain urgent orthopedic consultation

3.3.8 Acute Multisystemic Organ Failure

i. Evaluate for potential Multisystem organ failure (MSOF) all patients with VOC exhibiting severe deterioration
ii. Support with supplemental oxygen and mechanical ventilation when indicated in patients with respiratory failure.
iii. Manage acute renal failure with renal replacement therapy eg Dialysis
iv. Immediately consult hematologist or SCD expert and initiate simple or exchange transfusion (see SCD Transfusion guideline)

3.3.9 Stroke Secondary to Sickle Cell Disease

Stroke is one of the most devastating complications of SCD. The incidence of stroke is three hundred times higher in HbSS than HbAA children.

Risk Factors for Stroke in SCD:

a) Age (Children of 2-16 years of age are more commonly affected)
b) Blood velocity >200cm/s in distal internal carotid, middle or anterior cerebral artery

c) Previous Transient Ischaemic Attack

d) Steady state Hb < 7 g/dl or Neutrophils > 10 x 10^9/l

e) Nocturnal hypoxaemia ± Sleep apnoea

f) HbSS sibling with CVA (reflecting genetic factors)

Prevention of Primary Stroke:

a) All children aged 2-16 years should have trans-cranial ultrasonography (TCD USS) to identify those with a high risk of developing stroke.

b) Repeat TCD USS in 3 months in cases with a velocity of 170-199cm/s

c) In those identified with the high risk, stroke should be prevented with hydroxyurea or hypertransfusion (i.e. transfusion given every 3-4 weeks)

d) If bloodtransfusion is used, to be effective, the circulating HbS should be reduced to <30%

Features of Stroke in SCD:

a) Headache

b) Vomiting

c) Seizures, various sensory or motor neurological deficits: hemiplegia/paresis, paraplegia/paresis, monoplegia /hemiparesis, loss of hearing, etc.

d) Rarely, sudden reduction or loss of consciousness, or sudden death

e) Radiology: Magnetic Resonance Imaging may show acute infarct or bleed in the brain. Computerised Tomography usually can detect acute bleed, but may not detect a new infarct before ischaemic changes occur in the brain.

Differential Diagnoses of Stroke in SCD:

a) **Meningitis:** Patient may have reduced level of consciousness and/or fever

b) **Hypoglycaemia:** It is important to find out when the last meal was taken. It may present with jitteriness or seizure.

Management of Acute Stroke in SCD

a) Initial Assessment and Care:

- Brief history and physical examination; including the nervous system to distinguish between symptoms due to pain from those due to weakness (paresis or paraplegia)
- Stabilization, support, and monitoring of vital signs as necessary; maintain normal temperature
- Good oxygenation
- Careful hydration at two-third of the calculated maintenance volume in case the Syndrome of Inappropriate ADH Secretion (SIADH) secretion develops
- Hydroxyurea can be used if hypertransfusion is not feasible.

b) Laboratory Evaluation (Investigations):

- Full blood count with differential leucocyte and reticulocyte counts.
- Grouping and cross-matching of blood for transfusion (HbAA).
- Blood electrolytes, especially calcium, creatinine and urea.
- Tests for meningitis if suspected clinically; including lumbar puncture if considered safe.

Note:

- ***It is recommended to request for extended phenotyping of the patient for the 6 blood group antigens which most frequently cause development of antibodies: K, C, E, S, Fy and Jk.***
- ***Since it is standard practice to prevent recurrent stroke in the same patient by a long-term transfusion programme, every effort should be made to give the patient blood matched for these six antigens.***
- ***Consider initiation of disease modifying agent such as Hydroxyurea (hydroxycarbamide) (Refer to chapter…)***

c) Neuroimaging:

- CT scan as soon as possible to rule out hemorrhage
- MRI/MRA to define both parenchymal and vascular lesions. Diffusion-weighted MRI is highly sensitive in detecting early ischemic changes.

d) Red Cell Transfusion:

- Initially, this could be simple (top-up) or exchange transfusion; to be followed by a regular transfusion programme, preferably exchange, to keep the proportion of HbS below 30% in the patient's blood; indefinitely, to prevent Secondary Stroke.

e) Iron Chelation:

- It is important to monitor the body iron status in people on regular blood transfusion and start iron chelation when the serum ferritin concentration is 1000 ug/L or greater.

f) Non-medical Interventions and Rehabilitation:

- To improve quality of life of People Living with Sickle Cell Disease (PLWSCD), the use of devices that facilitate mobility, education and self-help skills should be put in place
- Dedicated stroke units and comprehensive rehabilitation centres should be established in Nigeria.

g) Iron Chelation:

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- Dedicated stroke units and comprehensive rehabilitation centers should be established in Nigeria.

Prevention of Primary Stroke in SCD:

a) In children ≤ 16yrs blood velocity ≥ 200 cm/s in the anterior or middle cerebral artery detected on two occasions 6 wks. apart is an indication for a transfusion programme to prevent Primary Stroke

b) Another indication for Primary Stroke prevention is occurrence of transient ischaemic attacks (TIAs). Hydroxyurea has now been found in a randomized clinical trial to prevent stroke.

CHAPTER 4
SPECIAL SITUATIONS

4.1 Hydroxyurea Therapy for Sickle Cell Disease

Of the estimated 1.2 million Nigerians living with SCD, less than 1% are on Hydroxyurea (HU).

Hydroxyurea which is contraindicated in pregnancy and in females looking to conceive is generally not found acceptable to Nigerians who have the USA standard indication of three or more episodes of sickle cell crisis per annum.

To identify people with SCD of such severity that the benefits of hydroxyurea justify potential risks, it is suggested that in Nigeria we use the criteria for hydroxyurea therapy outlined below, even though these are rather more stringent than standard ones used in the USA. Incidentally, the criteria below were used from 1998- 2006 when the drug was not licensed in the United Kingdom among over 600 SCD patients in St. Thomas‟ Hospital London who are predominantly of African ancestry and share cultural perceptions with Nigerians.

4.1.1 Suggested Indications for Hydroxyurea Therapy in Nigeria

a) $\geq$ 5 crises per year
b) 3-4 crises per year AND either neutrophil count $\geq$ 10 x 10^9 /L or platelet count $\geq$ 500 x 10^9 /L in steady state
c) Abnormal TCD > 200 cm/s
d) Acute Chest Syndrome; and
e) Stroke.

Note: ***The clinical decision to offer Hydroxyurea is favoured if the person does not want to have children or has completed his/her family.***

4.1.2 Contraindications

a) Pregnancy
b) Low Blood Counts:

- Neutrophils < 2 x 10^9/L
- Platelet < 100 x 10^9/L
- Reticulocytes (young RBCs) < 80 x 10^9/L

c) Liver Disease
d) Kidney Failure

Note: ***People on Hydroxyurea therapy must be monitored regularly for the above conditions as well as the HbF (Fetal Hemoglobin) level to assess response.***

Table 7: Benefits, Side-effects & Potential Risks of Hydroxyurea Therapy

Benefits	Side-effects	Potential Risks
↓ Crisis	↓ FBC	? Teratogenic (can lead to malformed babies)
↑ Hb Level (↓ blood transfusion)	↑risk of infections	? Mutagenic (can alter genes)
↓ Mortality	Dark coloration of nails	? Carcinogenic (can cause cancer)
	Nausea ± vomiting	
	Diarrhoea	

4.1.3 How Hydroxyurea Works in Sickle Cell Disease

a) ↑ Mean cell HbF

b) ↑ Red blood cells with detectable HbF (F cells)

c) ↓ Reticulocytes (RBCs ≤ 3 days old)

d) ↓ Neutrophils

e) ↓ Platelets

f) ↓ Adhesion of cells

g) ? ↑ Nitric oxide, a natural vasodilator.

4.1.4 Dosage of Hydroxyurea

a) 15mg/kg body weight/day which can be increased by 5mg/kg body weight/day at 3 – 4 week intervals (up to the maximum permitted dose of 35mg/kg body weight/day) until satisfactory clinical response occurs

b) There is no need to give the maximum tolerable dose (at which thrombocytopenia, neutropenia or reticulocytopenia develops) if good clinical response is achieved at a lower dose, bearing in mind that the higher the dose the greater the risk of undesirable side effects.

4.2 Prophylaxis and Antimicrobial Therapy

People with sickle cell disease are susceptible to infections due to a variety of causes. Infection is the dominant predisposing factor to sickle cell crisis and the commonest cause of death. Therefore,

prevention of infections and effective treatment of established episodes are very important aspects of the care of affected individuals.

4.2.1 Malaria Prophylaxis

The spleen plays an important role in the development of immunity against malaria. People living with SCD have functional asplenia or autosplenectomy, therefore, antimalarial prophylaxis is recommended with proguanil 100 mg daily for children up to 15years, and 200mg daily for adults [12,3]

4.2.2 Prophylactic Antibiotics

A controlled clinical trial showed that penicillin V is effective in reducing mortality from pneumococcal septicaemia associated with SCD[4]

a) Prophylaxis of penicillin V is recommended from the age of 3 months at a dose of 125 mg b.d up to 16 years
b) In adults, the dose is doubled to 250 mg b.d
c) For individuals allergic to penicillin, clarithromycin 250 mg b.d may be used
d) For people who continue to have recurrent infections (especially of the urinary or respiratory tract) while on penicillin V or clarithromycin, ciprofloxacin 250 mg b.d may be used.

4.2.3 Therapeutic Antibiotics

a) Once specimens have been taken for microbiology investigations, first-line medications should be chosen such as to cover for the common pathogens that cause infections in SCD
b) Effective staphylococcus and other gram-positive cover include: flucloxacillin, or sodium fusidate in patients allergic to penicillins
c) Effective salmonella and other gram-negatives cover include: oral ciprofloxacin at the therapeutic doses of 500 mg b.d or 750 mg b.d for severe infections; intravenous cefuroxime 750 mg t.d.s; or cefadroxil 500 mg b.d orally. All three are effective against salmonella organisms, which are second to staphylococci as the aetiological agents of osteomyelitis in SCD
d) Effective cover for anaerobes (which may cause infections in the mouth such as tooth abscess, or cholecystitis) is metronidazole
e) Microlides such as clarithromycin are effective cover for atypical organisms.

Note:

- ***Appropriate combinations of the above may be used as first-line antibiotics while microscopy, culture and sensitivity results are awaited***
- ***The definitive choice of drugs may be altered in the light of microbiology reports.***

4.3 Management of Osteomyelitis in Sickle Cell Disease

Osteomyelitis could have serious sequelae in PLWSCD. The acute form presents with features of inflammation over the affected bone which may include:

a) Pain
b) Warmth
c) Hyperaemia
d) Swelling
e) Oedema
f) Loss of function (restricted movement).

Note:

Differential diagnosis from bone infarction may be difficult not only because reactive inflammation may follow

infarction, but also bone infection could occur concurrently with infarction. In other words, acute osteomyelitis may co-exist with painful crisis involving the same bone.

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4.3.1 Investigations that Help to Detect Acute Osteomyelitis

a) Blood culture in search of pathogens that cause the bone infection
b) USS
c) MRI/PET

Note:

- ***The radiological techniques may reveal a (possibly purulent) fluid collection below the periosteum of the infected bone. Such sub-periosteal fluid requires urgent image- guided aspiration to prevent formation of a sinus from the bone to the skin; a characteristic feature of chronic osteomyelitis***
- ***The periosteal-skin sinus may develop in any infected bone, including the long bones of the limbs or the mandible. The other cardinal feature of chronic osteomyelitis is the presence of dead bone (sequestrum) lying within the infected bone***
- ***Sequestrum is detectable on plain x-ray because of the 'bone-in-bone' appearance it creates.***

4.3.2 Treatment of Osteomyelitis

a) Treatment of osteomyelitis in SCD requires an initial phase of intravenous administration of broad-spectrum antibiotics for 5-7 days
b) Followed by oral antibiotics for a recommended minimum period of 3-4 months; long enough to eliminate the causative organisms hiding within the dead bone
c) Once blood culture and other samples for microbiology have been taken, treatment is initiated with antibiotics effective for staphylococcus aureus and salmonella species – the two most common causes of acute osteomyelits in descending order of frequency among people who have sickle cell disease. An example of such an antibiotic combination is intravenous flucloxacillin 1g 6-hourly to kill staphylococcus aureus, and ciprofloxacin 500mg 12-hourly to kill salmonella.
d) The combination of antibiotics could be modified according to microbiological culture and sensitivity results, or the same combination continued orally for 3-4 months.

Note:

- ***Clinical experience has shown that it necessary to treat acute osteomyelitis in people with sickle cell disease for such a long time***
- ***This is because antibiotic therapy for much shorter periods (as in people who do not have SCD) fails to clear the pathogens in the infected bone, leads to chronic osteomyelitis, with bone and limb deformities.***

4.4 Blood Transfusion in Sickle Cell Disease

4.4.1 Simple (Top-Up) Blood Transfusion

Blood transfusion is indicated if:

a) There are acute symptoms of anaemia, such dyspnoea, tachycardia, severe weakness
b) Haemoglobin level is < 6g/dl
c) Haemoglobin level has dropped by > 2g/dl below the steady-state value.

Note: ***Because the cardiovascular system adjusts to the chronic anaemia, blood transfusion is not routinely indicated in steady state SCD simply for the reason that haemoglobin level is below 8-10g/dl.***

4.4.2 Exchange Blood Transfusion

Venesection to reduce the proportion of HbS red cells with transfusion of normal HbA blood is often beneficial in the treatment or prevention of life-threatening and other manifestations of sickle cell disease Hence, the aim in this process of exchange blood transfusion (EBT) is to reduce HbS to 30%.

Exchange blood transfusion can be done manually or automatically with a red cell apheresis machine.

Indications for Exchange Blood Transfusion:

a) Cerebrovascular Accidents (CVAs)
b) Acute Chest Syndrome (ACS)
c) Prior to major surgery
d) Multi-organ failure, including Systemic Marrow Fat Embolism (SMFE)
e) Multiple pregnancy
f) Prevention of recurrent stroke.

Relative Indications for Exchange Blood Transfusion:

a) Intractable or very frequent severe crises
b) Major priapism unresponsive to other therapy.

Preparation for Exchange Blood Transfusion:

a) Discuss objective of EBT with patient and obtain informed consent
b) Measure body weight
c) Coagulation screen to detect any bleeding tendency: Thrombin Time, Prothrombin Time, Activated Partial Thromboplastin Time and Platelet Count
d) Blood Chemistry including calcium level
e) Full Blood Count and percentage HbS
f) Group and Cross-match.

A. Manual Exchange Blood Transfusion

As a rough guide, 1 unit of blood /10 kg body weight (10 – 15mls /kg) is required for adults with Hb level up to 6g/dl. [6 7] Transfusion or removal of 1 unit of blood changes the haemoglobin concentration by 1 g/dl in the average adult.

Generally, a 6-unit exchange over 24 hrs is well tolerated. If more units of blood need to be transfused, it is advisable to spread the manual exchange over 48 hrs; and transfuse 3 – 4 units /day.

The Procedure. The fluid volumes stated below are for adult patients. In children, proportionately smaller volumes should be used depending on body weight.

a) Give 500 mls of dextrose saline (4.3% dextrose/0.18% saline in children) intravenously over 30 minutes

b) Remove 500mls of blood over 30 minutes

c) Give the 2nd bag of 500mls of dextrose saline over 30 minutes

d) Remove the 2nd unit (500mls) of blood over 30 minutes

e) Transfuse the 1st unit of red cell concentrate or blood over 1 hour

f) Remove the 3rd unit (500mls) of blood over 30 minutes

g) Transfuse 5 units of red cell concentrate over the next 20 hrs.

Note:

- ***The Hb level should not be increased above 11g/dl (Haematocrit > 0.33)***

- ***One or two units of blood could be removed by venesection with fluid replacement if the Hb level after the exchange is above 11g/dl***

- ***In patients with pre-transfusion Hb level of about 5g/dl who need manual EBT, there is no need for steps c to f above. In such situations, after giving 500mls of intravenous fluid and removing the 1st 500mls of blood, 5 units of red cell concentrate could be transfused over the next 20 hours (step g)***

- ***If the patient's pre-transfusion Hb level is 4g/dl or below, EBT is not necessary. Top- up transfusion of 6 units of red cell concentrate over 24 hrs will achieve the same end.*** [6]

B. Automated Exchange Blood Transfusion.

- EBT with an erythrocytopheresis machine is more efficient than the manual procedure in that it exchanges a larger proportion of the blood, is less tedious to patients and staff, and takes far less time to complete
- The procedure in children differs from that of adults in equipment and volumes/doses of agents
- Elective EBT in steady-state patients for non-acute indications, such as prevention of recurrent stroke, could be done as a day procedure
- Admission into a High Dependency Unit is advisable for EBT done as treatment of acute illness, e.g. acute chest syndrome

- The actual procedure should be done following the manufacturer‟s operating instructions detailed in the handbook of the particular apheresis machine used.

Post-Exchange Blood Transfusion Care:

- Considering that adverse events associated with EBT can occur late, it is advisable to observe the vital signs at 15-minute intervals for a minimum of half-hour after the procedure
- If a steady-state patient who was clinically stable before exchange is still unwell an hour after EBT is performed as a day procedure, admission into the ward may be considered for further observation and possible treatment
- In the absence of clinical problems, and vital signs are satisfactory 30 minutes after EBT, the femoral catheter may be taken out. Blood samples for post-transfusion FBC, percentage HbS, and chemistry should be taken from another peripheral vein to ensure more accurate results
- For acutely ill patients who had EBT in a HDU, the catheter used for the EBT may be left in-place for up to 5 days if required for other intravenous therapy. Blood samples for post-transfusion haematology and chemistry should then be taken 24 hours later, to allow time for optimal equilibration.

Management of Adverse Events Associated with Exchange Blood Transfusion:

Blood transfusion reactions and citrate toxicity are the usual complications.

a) Blood Transfusion Reactions

The features of a blood transfusion reaction include:

- Pain in the chest and back
- Rigors
- Skin rash
- Fever
- Bronchospasm
- Hypotension
- Shock with reduced urinary output.

The causes of blood transfusion reactions are:

- Incompatible red cell transfusion
- Reaction to leucocyte
- Platelet and plasma protein antigens
- Giving infected blood.

Treatment of Blood Transfusion reactions:

- The EBT should be suspended
- 10mg of piriton and 100mg of hydrocortisone should be given intravenously, and vital signs

closely monitored

- If there is hypotension, intravenous fluids should be given, the patient kept in a head- down position, and urinary output monitored
- Inotropes may be needed if the hypotension does not response to the measures above

- Disseminated intravascular clotting (DIC) can be triggered by immediate transfusion reaction. Therefore, a coagulation screen and fibrinogen assay will facilitate diagnosis
- The renal physicians should be invited to participate in the management if DIC is associated with acute renal shutdown
- If reaction against incompatible red cells is a differential, samples from the suspected units of blood (particularly the one being transfused when the adverse event started) should be sent to the laboratory with the patient‟s venous blood and urine samples for investigations.

b. Citrate Toxicity

Features of Citrate toxicity are:

- Hypocalcaemia – circumoral muscle twitching and paraesthesia
- Nausea, vomiting
- Chills
- Cardiac arrythmias
- Syncope.

The cause of Citrate toxicity:

- Citrate toxicity may complicate EBT if intravenous Calcium Gluconate is not given prophylactically.

Prevention and treatment of citrate toxicity:

- It is pertinent to bear in mind that severe hypocalcaemia may occur without fore- warning by the symptoms above
- The complications can be prevented by keeping patient warm and blood should be pre-warmed
- The patient should be informed about the symptoms and advised to immediately call the attention of hospital staff if they occur
- It is unusual for citrate toxicity to develop during EBT if calcium gluconate is given in the middle of the procedure as stated previously
- Should it occur before the calcium gluconate is given, or despite doing so half-way through the EBT, the exchange should be discontinued
- Calcium gluconate (2mls of 10% solution) should be given over 5 minutes
- The procedure can be resumed when the clinical and ECG features of hypocalcaemia have resolved. Increasing the total procedure time should be considered when the EBT is resumed, and on subsequent exchanges in the same person.

4.5 Peri-Operative Management of Patients with Sickle Cell Disease

It is important to note that all patients going for elective surgical procedures should have their genotype done, while those for emergency surgeries should have their full blood count, peripheral blood film, sickling solubility test or electrophoresis done. This will give a picture of their genotype.

4.5.1 Using General Anaesthesia

a) Surgery requiring general anaesthesia may increase the risk of vaso-occlusive events in SCD

b) Surgical trauma and the inflammatory response to tissue injury, hypoxia associated with general anaesthesia, and dehydration from reduced oral fluid intake; all are recognized precipitating factors for sickle cell crisis and other vaso-occlusive manifestations of the haemoglobinopathy

c) It is therefore necessary to take appropriate preventive or therapeutic measures in SCD patients and individuals at risk of carrying the gene for HbS

d) If the Hb level and blood film are normal, and the sickle solubility test is negative in a patient older than 6 months who was not transfused in the previous 4 months, sickle cell disease or trait is unlikely. Therefore, peri-operative management could be carried out as for HbAA individuals

e) Sickle cells in the peripheral blood film, low Hb level and positive sickle solubility test are highly suggestive of SCD, and the patient should be treated accordingly

f) A positive sickle solubility test with normal Hb level and normal blood film may be found in sickle cell trait.

g) In emergency situations when the Hb genotype cannot be confirmed, it is recommended that peri-operative management is carried out as if the patient had SCD. This recommendation also applies to situations in which the patient had blood transfusion in the previous 4 months, and the sickle solubility test is negative with normal blood film and Hb level

h) However, the percentage HbS needs to be less than 20% for the sickle solubility test to be negative, and peri-operative clinical problems related to HbS are unlikely to arise in such situations

i) The situation is similar to that of SCD patients with HbS maintained below 30% by regular exchange blood transfusions, who seldom develop new vaso-occlusive clinical problems.

Note:

- ***It is necessary to determine the Hb genotype as soon as it is possible in all patients who could not have it done before emergency surgery***
- ***The low probability of HbS-related clinical problems notwithstanding, it is important to bear in mind that false negative results of the sickle solubility test may be obtained in HbSS infants aged less than 6 months before HbF is substantially replaced by HbS; and in HbAS or HbSS adults following blood transfusion***
- ***In previously transfused patients, accurate Hb genotype may not be obtainable from blood tests until 4 months after transfusion***
- ***DNA analysis can provide reliable results of Hb genotype within 4 months of blood transfusion***

- ***Patients who were not transfused, including infants aged less than 6 months, can still have accurate determination of Hb genotype on blood samples***
- ***If an individual was transfused peri-operatively, a pre-transfusion blood sample taken during the episode of illness can be used for haemoglobin genotyping.***

4.5.2 Blood Transfusion

a) Exchange blood transfusion to achieve HbS below 30% and Hb level 10 – 11g/dl is recommended before major surgery such as hip replacement, complex neurosurgical, abdominal or thoracic operations, and tonsillectomy

b) For not so major surgery such as caesarian section and cataract removal, top-up blood transfusion to a haemoglobin level 10 – 11g/dl will suffice[7] SCD patients are prone to red cell antibody formation [8]. It is therefore important to request for blood a minimum of 1 day before the planned transfusion so there is ample time to obtain compatible units of blood.

4.5.3 Oxygen Therapy

a) Hypoxaemia predisposes to sickling, and its prevention by oxygen administration is of paramount importance in the peri-operative management of SCD patients

b) Oxygen may be required from the time of pre-medication, especially if respiratory depressant drugs have been given

c) Pre-oxygenation is essential before the induction of anaesthesia

d) A higher than standard oxygen concentration in the anaesthetic gases is used during surgery

e) Oxygen administration is continued post-operatively until the patient starts to mobilize or through the first day

f) In view of the usual drop in oxygen saturation during sleep, the inhibition of respiratory (breathing) movements because of post-op pain in the thorax or abdomen and the tendency of vaso-occlusive events in SCD to develop at nights, it is advisable to administer oxygen in the 2^{nd} – 4^{th} nights after surgery in the thorax or abdomen

g) Monitoring the blood oxygen saturation peri-operatively with a pulse oximeter or by measuring arterial blood gases, helps ensure that hypoxia is prevented; or detected and treated.

4.5.4 Hydration

a) SCD is associated with inability to concentrate urine resulting in increased tendency to dehydration

b) Therefore, SCD patients undergoing surgical procedures should be given sufficient IVF such as 5% dextrose or D/S to maintain adequate hydration.

4.5.5 Hypothermia

Exposure to cold frequently precipitates Sickle Cell crisis. Hypothermia during surgery may stimulate reflex shivering early in the post-operative period, peripheral vaso- constriction, increased oxygen consumption by skeletal muscles, tissue hypoxia, sickling and vaso-occlusive crisis. To prevent these, it is crucial to ensure that the body temperature is maintained at normal values during surgery in SCD patients.

4.5.6 Sickle Cell Trait

a) For sickle cell trait, there is no evidence of a clinically significant increase in the risk of general anaesthesia to HbAS individuals. However, there is possibility of red cell sickling and vaso-occlusion if severe hypoxaemia occurs in HbAS patients under general anaesthesia

CHAPTER 5

SICKLE CELL DISEASE AND PREGNANCY

5.1 Introduction

Sickle cell crises are unpredictable in or out of pregnancy though there are well known precipitating factors such as hypoxia, trauma, acidosis, cold, dehydration, alcohol, infection and blood stasis.

Physiological changes of pregnancy that are relevant to SCD include: increased plasma volume, increased red cell mass, decreased peripheral resistance, a sizeable low resistance uteroplacental circulation, less physical movement and an increasing abdominal mass. In addition, there is an increased risk of venous thromboembolism, especially in the puerperium.

Pregnant women become acidotic more easily and have a tendency to urinary tract infections. Labour, delivery, haemorrhage and interventions, such as vaginal examinations or surgery, can cause dehydration and infection. Thus, pregnancy and childbirth are risk factors for precipitating crises.

A problem with the clinical features is that there is overlap of pathological and physiological symptoms of pregnancy. There should be a low threshold for investigating if there is a clinical suspicion. A particularly difficult differential diagnosis is that of chest pain or breathlessness especially if the expectant mother is ill.

5.2 Effects of Sickle Cell Disease on Pregnancy

a) Pregnancy-induced hypertension and pre-eclampsia. In this case, uterine artery doppler ultrasonography is useful for diagnosis and may detect notching or high resistance indices.
b) Renal manifestations of SCD are common during pregnancy. These include haematuria, progressive inability to concentrate urine, and subtle proton and potassium secreting defects. The urinary concentration defect makes pregnant women with the sickling disorder more prone to dehydration.
c) Labour (particularly if prolonged or induced) is related to stasis, dehydration and infection. Induction at 37 completed weeks is advisable to prevent foetal loss. Elective Caesarean Section (CS) is not offered as a routine, partly as it is associated with at least 30% higher severe maternal morbidity even when compared to labour with high emergency CS rates.
d) The patient may have chest pain or tenderness. Apart from bone pain crisis involving the ribs (elicited by tenderness over the ribs) it could be due to a simple chest infection, acute chest syndrome, pneumonia or pulmonary embolus. Although investigations such as ECG, Chest X-Ray, blood gases and ventilation-perfusion

scans may be diagnostic, in some occasions, pathologies may co-exist or patients may be so sick that "blunderbuss" treatment for all three may be warranted.

5.3 Documented Complications of Pregnancy with Sickle Cell Disease

a) Miscarriage
b) Urinary tract and pulmonary infections
c) Malaria
d) Intrauterine growth restriction
e) Pre-eclampsia
f) Preterm labour and delivery
g) Fetal distress
h) Multiple antenatal admissions
i) Raised caesarean section rates
j) Puerperal sepsis
k) Thrombosis
l) Obstetric bleeding.

Note:

- *Although the severity of SCD in the non-pregnant state is related to the manifestation during pregnancy, it is unpredictable.*
- *HbSS state is generally considered to cause the most severe SCD. The other common variant, HbSC disease has similar, although less severe manifestation in the non-pregnant state. However the outcome of pregnancy in HbSC women is not necessarily more favorable.*
- *The demands of multiple pregnancies make this particularly risky in SCD. Comprehensive and multidisciplinary care improves outcome of pregnancy in SCD.*

5.4 Multidisciplinary Team Approach to the Management of Sickle Cell Disease in Pregnancy

We have no doubt that pregnant women with SCD should be cared for in centres where all the relevant expertise is available as these are high-risk pregnancies. Hence, the importance of a multidisciplinary approach cannot be overemphasized.

The composition of the team involves many professionals such as the:

a) Haematology doctors and nurses
b) Obstetrician and midwives
c) Genetic counsellors
d) Laboratory sickle cell specialists
e) Psychologists
f) Anaesthetists

g) High dependency and intensive care treatment teams.

Note:

- *Aside from the membership of the team, frequent non-hurried communication about individual patients, protocols, clinical errors and learning, audit and research must be fostered*
- *There should be updated evidence-based protocols and joint multidisciplinary meetings to maintain high standards of care and effective communication between the team members*
- *An atmosphere of mutual respect must be encouraged among the different expertise brought to the management of these patients with a complex chronic medical disorder and yet simple and understandable desires for parenting.*

5.5 Pre-Conception Counselling

a) It is ideal to see women with SCD pre-conceptually in order to discuss the risks involved and plan the management of pregnancy

b) If the partner‟s status is not known it can be checked and prenatal diagnosis can be discussed. The need for early booking can be encouraged

c) In some cases, it would be prudent to advice against pregnancy if the risks for the woman are significant even before she embarks upon a pregnancy. Although it is very painful to consider voluntary infertility, having to consider a termination during a planned or wanted pregnancy is also dreadful.

5.6 Pre-Natal Diagnosis

a) Cells or tissue for antenatal diagnosis can be obtained by chorionic villous sampling (CVS) between 10-12 weeks gestation, or by amniocentesis or fetal blood sampling in the late second trimester
b) With all invasive procedures, there is 1-2% risk of procedure related loss of the pregnancy
c) Prenatal diagnosis can be performed by DNA analysis with the polymerase chain reaction (PCR) and Southern blotting
d) Pre-implantation genetic diagnosis (PGD) is an alternative and powerful diagnostic tool for identifying sickle cell status in embryos that uses assisted reproductive techniques in conjunction with modern molecular methods
e) With PGD, the genetic status of an embryo can be determined before transfer into the uterus after in-vitro fertilization. This virtually eliminates the risk of bearing a child with the disease
f) Although prenatal testing is currently available, some couples have strong personal objections to aborting affected fetuses. For these couples, PGD provides a realistic alternative to prenatal testing
g) Developing techniques such as detection of fetal biomakers in maternal blood as a means of determining the baby‟s Hb genotype could be explored.

5.7 At Booking

a) Women with SCD (and their families) should be advised regarding the increased risk of crisis, intrauterine growth restriction, pre-eclampsia, fetal loss and sickling in uteroplacental circulation
b) Women should be advised that coping with crises at home is not appropriate during pregnancy particularly because of the need to monitor the fetus
c) They should be encouraged to have a low threshold for admission if they think they are starting a crisis
d) An early dating scan is arranged so that accuracy of dates is confirmed and monitoring of growth and timing of delivery can be planned
e) Hyperemesis in early pregnancy can be a problem, so early prevention of dehydration and control of nausea may reduce the risk of painful episodes in early pregnancy.

5.8 Ante-Natal Care

a) As this is a high-risk pregnancy a more frequent schedule of care should be planned between the obstetrician, haematologist and specialist midwives
b) Iron supplementation may be required, but only if the serum ferritin levels are low
c) A monthly haemoglobin check should be made and midstream urine should be sent monthly for culture and sensitivity
d) The fetus should be monitored closely as there is a higher rate of intra uterine growth retardation (IUGR) and higher perinatal mortality

e) After the early dating scan anomaly, ultrasound scan is done at 20 weeks with intrauterine artery Doppler. This is followed by growth scans at 26, 30, 34 and 38 weeks
f) Scans may be performed more frequently if there are concerns about growth or liquor volume
g) It is vital that mother understands the risk factors and that there is an open-door policy 24 hours 7 days a week for admission if in pain, sickle cell crises, dyspnoea, pre-eclampsia or any need for blood transfusion
h) Ante-natal testing of the baby‟s father for haemoglobinopathy is indicated in HbSS expectant mothers if the father is HbAS, then the couple should be offered prenatal diagnosis for SCD.

5.9 Prophylactic Transfusion

a) This might be considered in an effort to avoid the risks of crises in pregnancy.
b) Evidence from randomized studies showed that there is a reduction in the episodes of third trimester crises but no improvement in neonatal outcome.[10 11] Transfusion during pregnancy should be reserved for women with twins, previous poor obstetric history, chest crisis, recurrent crises and severe anaemia.

5.10 Admission Criteria

Indications for hospital admission for pregnant patients with sickle cell disease in crisis are as follows:

a) Suspected pulmonary, neurological, splenic or hepatic complication
b) Pain that does not resolve after 4-6 hours despite good analgesia which would include narcotics
c) Inability to maintain adequate hydration if discharged home; e.g patients who are vomiting.
d) Fever or any other evidence of infection.
e) Uncertain diagnosis

5.11 Discharge Criteria following Treatment for Sickle Cell Crisis

a) Pain relief after 4-6 hrs in the Emergency department
b) Stable cardio-respiratory status
c) Stable haemoglobin
d) Absence of fever
e) Assurance of continued care at home.

5.12 Intrapartum

a) The aim of intrapartum management in SCD is to achieve a safe vaginal delivery when possible.

b) Due to increased perinatal mortality, aim for delivery between 38-40 weeks by induction of labour (IOL). However the risk-benefit should be individualized as failed IOL can lead to emergency caesarean section and problems in subsequent pregnancies where IOL is relatively contraindicated in previous scar.

c) The mother should be well hydrated and oxygenated throughout labour.

d) The fetus should be monitored by continuous cardiotocograph, as there is increased risk of fetal distress in labour.

e) Epidural is preferable to general anaesthesia if operative intervention is needed. It is important to avoid hypotensive episodes as these may precipitate a vaso-occlusive crisis.

f) There is an increased risk if postpartum haemorrhage occurs with a background of chronic anaemia and thus the third stage should be actively managed with an oxytocic.

g) Attention to blood loss is especially important if women have become difficult to cross-match or transfuse through the development of antibodies.

h) Throughout labour and delivery a senior midwife and doctor with knowledge of the condition should be responsible for her care so that appropriate timely intervention and management is possible.

5.13 Postpartum

a) Thromboprophylaxis with TED (thromboembolism) stockings and low molecular weight heparin should be considered postnatally, especially with any other risk factor (such as high BMI, operative delivery, high platelet count, HbSC).

b) Early ambulation should be encouraged.

c) Postpartum antibiotics should be given for operative deliveries and there should be a low threshold for treating a suspected infection.

d) The mother should be encouraged to keep well hydrated.

e) The baby should be screened for haemoglobinopathy if prenatal diagnosis was not possible.

f) Cord blood can be collected for screening of the neonate.

5.14 Contraception

Should be discussed and can be prescribed before discharge.

a) There is need for effective contraception to space or limit the family size

b) Progesterone only pills/injectable/implants are effective & have some added advantages (reduced menstrual blood loss & reduced frequency of sickling /crises)

c) Sterilization

d) Barrier contraception. e.g. male condom

e) **AVOID** combined oral contraceptive pills and Copper-T intrauterine contraceptive device (IUCD).

CHAPTER 6

MANAGEMENT OF CHRONIC COMPLICATIONS OF SICKLE CELL DISEASE

6.1 Introduction

Chronic complications of SCD may occur following acute episode or as chronic or as recurrent event. These complications my occur early in life and span the entire life of individuals affected by SCD. Some of the common chronic complications may include, chronic pain cholelithiasis, renal dysfunction, musculoskeletal, cardiovascular and pulmonary hypertension.

Chronic complications of SCD include the following:

i. Avascular necrosis
ii. Cardiac complications
iii. Chronic hypersplenism (A1,nA2)
iv. Chronic Pain
v. Endocrine complications
vi. Gastrointestinal complications
vii. Leg Ulcers
viii. Nocturnal enuresis
ix. Ophthalmologic Complications
x. Psychological complications
xi. Pulmonary Hypertension
xii. Renal Complications
xiii. Seizures under neurological complications
xiv. Stuttering/Recurrent Priapism

6.1.1 Osteonecrosis (Avascular Necrosis) Clinical features:

a) Patients with osteonecrosis (avascular necrosis of femoral head usually present with pain in the hip or groin and difficulty in walking. The disease is already bilateral in about 40% of such patients
b) Examination will reveal a hip that is painful on movement with restricted range and shortening if unilateral
c) In the early phase, the patient may also complain of knee pain which is a referred pain from the hip
d) Many patients with shoulder osteonecrosis present late because the joint is non- weight bearing and they tend to cope with moderate pain.

Diagnosis:

a) Clinical presentation
b) X-ray shows bone sclerosis, bone collapse and secondary osteoarthritis
c) MRI early in the course

Management:

Can be Non-Operative and/or Surgical management.

a) Non-Operative:

- Counsel patient to minimize movement and bearing heavy weight on affected joint
- Pain management with the use of Paracetamol, Non-Steroidal Anti-Inflammatory

Agents and/or Opiates such as Codeine and Tramadol.

- Give disease modifying therapy such as hydroxyurea to prevent progression or involvement of other joints
- Refer for Orthopedic assessment, treatment, and for surgical management

b) Surgical management:

- Patients with chronic orthopaedic complications of SCD should be referred early to an orthopaedic surgeon for assessment and continued management.

6.2 Cardiac complications

i. Assess all patients for cardiac symptoms (dyspnea, dizziness, chest pain, ankle swelling) and perform cardiac examination that includes assessment for signs of right heart strain at each annual review

ii. Patients with cardiorespiratory symptoms and signs should be evaluated with electrocardiography (ECG) and echocardiography

iii. In patients with sickle cell disease echocardiography should be performed at initial presentation to adult service and at least once every three to five years even in asymptomatic patients (or earlier if patients are symptomatic or hypoxic).

iv. Echocardiography should be repeated annually in patients with previously elevated tricuspid regurgitant jet velocity (TRV) who have not had right heart catheterization (RHC).

v. Patients should be referred to a pulmonary hypertension specialist center for consideration of RHC if: TRV >290 cm/sec; or, TRV 250-290 cm/s and symptoms suggestive of pulmonary hypertension.

6.3 Chronic Hypersplenism

This is a chronic splenic sequestration associated with enlarged spleen, cytopaenia with anaemia and reduction in white blood cells and platelets. The anaemia is usually chronic in nature and patients seldom present with signs of heart failure.

Symptoms/signs:

i. Pallor, lethargy
ii. Chronic splenomegaly manifesting as abdominal distension
iii. Cytopaenias

Immediate action:

Assess and document size of liver and spleen, mark on abdomen

Investigations:

i. Full blood count,
ii. Reticulocytes
iii. Peripheral smear
iv. Creatinine, urea, electrolytes, liver function tests, LDH
v. Blood cultures
vi. Malaria rapid test and film for malaria parasites
vii. Iron studies
viii. Bone marrow aspirate

Management:

i. Exclude and treat all causes of anaemia
ii. Review after 3 months

iii. Monitor spleen size and document at every visit
iv. Refer to surgical department for elective splenectomy
v. Therapeutic splenectomy is indicated if >2 episodes of sequestration

Gastrointestinal complications

1. Acute Abdomen

a) Investigations:

i. Blood culture; ii. Serum amylase; iii. Abdominal ultrasound scan; iv. Abdominal x-ray ; v. CT scan

b) Management:

i. Manage conservatively if sickle cell disease-related
ii. Ensure early consultation with surgical team
iii. Develop policies on antibiotics and indications of endoscopy in collaboration with the microbiologists and gastroenterologists for the management of gall stones and other complications

2. Mesenteric (Girdle) Syndrome

Recommendations:

i. Rule out other surgical pathologies
ii. Manage conservatively with Intravenous fluid, analgesics and nasogastric aspiration if vomiting
iii. Consider exchange blood transfusion

3. Chronic Sickle Hepatopathy

Recommendations:

i. Consider exchange red cell transfusion programme
ii. Refer to a specialist center with exercise in sickle cell hepatopathy

4. Viral Hepatitis

Recommendations:

i. Refer to hepatologist
ii. Monitor haemoglobin concentration in patients on ribavarin because of the risk of hemolytic anemia

5. Iron overload

Recommendations:

i. Ensure iron overload monitoring in patients receiving repeated red cell transfusion

6. Chronic Pain

SCD pain is considered chronic if it lasts more than 3 months. Determine the cause and type of SCD-related chronic pain. This includes chronic pain with objective signs such as avascular necrosis (AVN) and leg ulcers, and chronic pain without objective signs due to neuroplasticity of the peripheral or central nervous system.

Assess all people with SCD for chronic pain annually or more often as needed. This assessment should include descriptors of the pain, its severity on a numerical scale, its location, factors that

precipitate or relieve it including biopsychosocial factors and its effects on the patient's mood, activity, employment, quality of life and vital signs

6.1 Management:

i. Use a combination of the patient's response to treatment—including pain relief, side effects, and functional outcomes to guide the long-term use of opioids
ii. Use long- and short-acting opioids to manage chronic pain that is not relieved by nonopioids.
iii. Encourage people receiving opioids to increase their fluid intake, maintain high dietary fiber intake and to use stool softeners and bowel stimulant laxatives such as senna as needed.
iv. Encourage people to use deep tissue/deep pressure massage therapy, muscle relaxation therapy, and self-hypnosis
v. Consider management of neuropathic pain by antineuralgic, tricyclic antidepressants, e.g., amitryptiline
vi. Patients with progressive musculoskeletal conditions should be referred to orthopedic or rheumatology specialist
vii. Refer for evaluation by psychologist - to relieve anxiety / depression stemming from disability, job absences or financial difficulties
viii. Refer to occupational therapist and physiotherapist to assist patients to gain optimum physical function and independence

7.0 Endocrine Complications

1. Gonadal Dysfunction (low testosterone)

a. Evaluation:

i. Measure weight and height and plot on an appropriate growth chart.
ii. Screen levels of testosterone (early morning total testosterone, 2 separate readings before
10:00am

b. Management:

i. If at the age of 14 in male patients there is evidence or symptoms of hypogonadism refer to endocrinologist for evaluation and treatment.

2. Adrenal Dysfunction

i. Evaluate patients who have hemodynamic compromise during sickle cell crises with sepsis for
adrenal insufficiency
ii. Refer to endocrinologist if there is evidence of adrenal insufficiency.

3. Thyroid Dysfunction

a. Evaluation:

i. Check for history of chronic transfusion, a recognized risk factor of hemosiderin-associated thyroid dysfunction

ii. Obtain annual thyroid screening for such patients

b. Management:

i. Refer to endocrinologist if there is evidence of hypothyroidism.

4. Impaired glucose tolerance and diabetes mellitus

i. Perform annual glucose tolerance screening with fasting plasma glucose in chronical transfused SCD patients

ii. Refer SCD patients with impaired glucose tolerance and diabetes mellitus to endocrinologist

5. Parathyroid dysfunction

a. Evaluation:

i. Screening with serum calcium, phosphorus, alkaline phosphatase, parathyroid levels, and neck ultrasound to exclude hyperthyroidism

ii. Screen for hypothyroidism in chronically transfused SCD patient from 10 years of age

b. Management:

i. Refer patient with evidence of parathyroid dysfunction to the endocrinologist.

8.0 Management of Chronic Leg Ulceration in Sickle Cell Disease

Chronic leg ulceration occurs in less than 10% of people with SCD in West Africa including Nigeria, usually in patients who are older than 12 years. It is commoner among the male patients with low steady state Hemoglobin level.

Clinical Features:

i. Typical ulcerations are situated around the medial or lateral malleolus of one or both ankles

ii. It arises spontaneously, although a history of preceding trauma may occasionally be obtained from the patient

iii. Healing is very slow and recurrence or breakdown of healed ulcers is very common.

Treatment:

This requires multidisciplinary approach involving Hematologist, Plastic and orthopaedic surgeons and Specialist Nurses

a) Daily wound dressing
b) Rest and elevate the affected limb
c) Treat any associated infection
d) Autologous skin graft.
e) Give zinc supplementation
f) Apply graduated compression bandages to reduce lymphoedema
g) Elevate feet when sitting to improve blood circulation to the ulcer
h) Treat the pain with adequate and appropriate analgesia. Usually, the pain is

neuropathic in nature and it is treated with amitriptyline or newer antiepileptic drugs. (see pain management in SCD guidelines)

i) Take biopsy for histopathology when malignancy is suspected.
j) Consult vascular surgeons if features of arterial insufficiency present.
k) Consider regular or exchange blood transfusion until the wound heals if the above measures fail.
l) Consider discontinuation of Hydroxyurea in patients with non-healing or slowly healing ulcer.
m) Explain to the patient that ulcer may take long time to heal. Also, enforce the prevention measures to reduce the risk of recurrence.

8.1 Factors that Promote Healing Leg Ulcers:

a) A clean wound
b) Daily dressings to keep the surface fresh and clean,
c) Rest.

8.2 Factors that Deter Healing of Leg Ulcers:

a) Walking and running long distances
b) Infection of ulcer surface
c) Scabs on the ulcer surface
d) Underlying osteomyelitis**.**

9.0 Nocturnal Enuresis

Children with SCD and sometimes adults (between the ages of 18 &20) do experience nocturnal enuresis. It contributes to decrease health related quality of life in people with SCD resulting in low self-esteem and occasionally, social isolation.

Postulated Causes:

i. Hyposthenuria leading to nocturnal polyuria
ii. Decrease bladder capacity or nocturnal bladder over activity
iii. Increase arousal thresholds
iv. Sleep disorder breathing.

Management:

i. Routinely ask parents about nocturnal enuresis in the child with SCD aged 6 years and older
ii. Document presence of enuresis and give information to parents and other caregivers.
iii. Assure parents that nocturnal enuresis is a known and common complication of SCD
iv. Behavioral modification through alarm therapy
v. Investigate presence of snoring, possible obstructive sleep apnea, and nocturnal hypoxemia; if these are present, refer child to ENT surgeon for further evaluation and management.
vi. Refer child to enuresis management program, if one exists, for training in use of enuresis alarms, and provide family counseling to avoid punitive measures that further lower the child's self-esteem.
vii. Try oral of nasal desmopressin if other methods fail.
viii. Do not withhold fluid intake in management of enuresis in children with SCD.

10.0 Management of Ocular Complications in Sickle Cell Disease

Eye complications can occur in sickle cell disease but are more common with HbSC. This may be the first indication that the patient has SCD. Ocular complications include non- retinal and retinal lesions.

Symptoms:

The ocular symptoms of SCD include:

- Swelling of the eyelid
- Protrusion of the eyeball
- Droopy eyelids
- Ocular redness
- Yellowness of the eyes
- Crossed eyes
- Ocular aches
- Floaters (appearance of dots or cobwebs which move along with patient’s gaze)
- Flashes of light
- Sudden loss/gradual deterioration of vision

Signs:

Reduced vision or loss of vision (blindness) (measured objectively using Snellen‟s chart).

Treatment:

a) Treat underlying condition e.g. systemic infections, dehydration e.t.c.
b) Start antibiotic eye drops and/or ointments (especially if presenting with lid swelling or discharge).
c) Reassure patient
d) Refer to an Ophthalmologist immediately
e) Encourage regular eye examination once in 2 years for all HbSS patients and once yearly for all HbSC patients.

11.0 Psychological Complication

i. Conduct psychological assessments for all patients (children, adults) routinely
ii. Conduct neuropsychological assessments when neurological complications and/or educational problems are indicated
iii. Assess mood and emotional problems
iv. Assess physical and social function
v. Assess coping strategies in relation to pain, symptoms and complications
vi. Assess general health and related quality of life
vii. Assess attention/concentration and executive function initially, followed by comprehensive neuropsychological assessments
viii. Offer psychological therapies e.g., cognitive behavioral therapy (CBT): individual and/or group or family sessions as appropriate
ix. Suggest available psychological self-help resources including internet-based interventions
x. Liaise with schools and colleges to negotiate additional or special educational support to compensate for neuropsychological complications and poor school performance
xi. Refers to counsellors (clinical psychologist) and psychiatrist

11.0 Pulmonary Hypertension

Evaluation:

i. Screening tests: Obtain echocardiography, measure N-terminal pro-brain natriuretic peptide (NT-proBNP), and/or 6-minute walk distance (6MWT). If pulmonary arterial pressure (PAP) is > 40mmHg or tricuspid regurgitation jet velocity (TRV) is >2.5m/sec or NT-proBNP is >164.5pg/mL and/or low 6MWT is ≤ 333m do confirmatory test
ii. Confirmatory test: Perform right heart catheterization
iii. Treatment: If the mean pulmonary arterial pressure (mPAP) is > 25mmHg Consult Pulmonary hypertension expert for treatment using target therapies such as: prostacyclins analogues, phosphodiesterase type 5 inhibitors or endothelin receptor antagonists

12.0 Management of Renal Complications in Sickle Cell Disease

Renal complications are common in SCD and should be looked out for. They can be precipitated by prolonged use of non-steroidal analgesics.

Clinical Features:

- There is failure to concentrate urine (hypostenuria) leading to frequent urination
- Patients are therefore susceptible to dehydration during severe pain crisis and before general anaesthesia when they are unable to drink

- Haematuria (blood in urine) may occur in sickle cell anaemia (HbSS) and is due to renal papillary necrosis. Frank haematuria can be alarming and the health worker should reassure the patient and family that it is self-limiting and has a good prognosis.

- Enuresis: Since young children may have prolonged bed wetting (enuresis), the caregiver/parent should encourage them and supervise them to ensure that they empty their bladder at bedtime. The health worker should reassure the care giver/parent in this task and when severe, drugs such as vasopressin may be given to the children.

Treatment:

a) Patients with haematuria should be referred to a secondary or tertiary health facility for exclusion of other causes
b) Admit to the hospital
c) Encourage high fluid intake: 4 to 5 litres per day with frusemide 40 mg twice daily in adults; and 100-150ml/kg/day with 1mg /kg of frusemide in children. The increased urinary volume helps to prevent blood clots in the urinary tract
d) Alkalinize of the urine with sodium bicarbonate
e) When blood loss is profuse, replacement blood transfusion may be needed.

Note:

- *Chronic renal failure may be seen in some adolescent or adult patients and should be suspected when there is systemic hypertension (otherwise rare in SCD) or persistent severe anaemia or proteinuria*
- *Dip stick test of urine should be done twice yearly*
- *Those with albuminuria should be referred for proper evaluation.*

13.0 Seizure Under Neurologic Complication

i. Evaluate children and adults who present with new onset seizure for acute stroke or evidence of cerebrovascular disease. (See "Acute Stroke" above.)
ii. Evaluate children and adults who present with new seizure and no evidence of stroke for other causes of seizure such as epilepsy
iii. Consult with neurologist to manage chronic (recurrent) seizure with appropriate anticonvulsants.
iv. Do not give meperidine (pethidine) to people with SCD who have a seizure disorder; a metabolite, normeperidine (norpethidine), a neurotoxin, is associated with seizures.

14.0 Stuttering/Recurrent Priapism

Diagnosis:

i. Take history of frequency and duration of erections and examine the phallus
ii. Do corporal blood gas analysis and corporal Doppler ultrasound

Management:

i. Institute simple measures such as bladder emptying, hot bath, hydration, adequate analgesia (NSAIDs and opiates) and gentle exercise
ii. Consult Urologists if no detumescence after 2 hours for evaluation and possible surgical intervention.

Prevention:

i. Give slow oral etilefrine starting with 25mg daily nocte. If there no satisfactory response, increase dose by 25mg every 2 weeks to a maximum of 100mg in divided doses or oral pseudoephedrine 30mg nocte in children of less than 10 and 60mg nocte in adults and children above 10 years
ii. Consider the use of Hydroxyurea
iii. Educate male patients and parents of adolescent patients about the risk and the emergency nature of priapism, self-treatment measures and to seek medical help if episode exceeds 2 hours.

CHAPTER 7

CARE IN STEADY STATE OF SICKLE CELL DISEASE

7.1 Introduction

Patients with SCD are best cared for in comprehensive care setting with a multidisciplinary team of healthcare workers. The goal of care is to ensure that the affected individual remains in a steady-state, leads a happy and fulfilled life, free from sickle cell crises, debilitating complications, and untimely death.

During routine visits the following clinical evaluation should be carried out:

a) History taking

b) Complete physical examination and look out for pallor, jaundice, fever, hepatomegaly, splenomegaly, leg ulcers, etc.

c) Dipstick for albuminuria.

7.2 Routine Prophylactic Measures

7.2.1 Malaria Prevention

Malaria is associated with ill-health and deaths in malaria-endemic areas such as Nigeria. Therefore, malaria prevention is crucial in the care of PLWSCD.

The following are some measures that can help reduce the frequency of malaria:

a) Anti-malarial prophylaxis:

- Proguanil tablets: should be given as shown in the table below:

Age	Dose
Under 1 year	¼ Tablet (25mg) daily
1 – 4 years	½ Tablet (50mg) daily
5 – 8 years	1 Tablet (100 mg) daily
9 – 14 years	1 ½ Tablets (150 mg) daily
Over 14 years	Adult Dose daily

The daily dose is best taken with water, after food, at the same time each day.

Provided the tablet fragment gives the minimum amount specified, precise accuracy in children's dosage is not essential since the drug possesses a wide safety margin. For a young child, the dose may be administered crushed and mixed with milk, honey or jam.

Older people: There are no special dosage recommendations for the elderly, but it may be advisable to monitor elderly patients so that optimum dosage can be individually determined.

However, because of poor compliance, Intermittent Preventive Medicine was advanced as shown in (b) and (c) below:

b) Intermittent Preventive Treatment (IPT): This consist of a bi-monthly course of treatment with mefloquine-artesunate (MQ+AS).

This treatment is given once daily for 3 days. Patients weighing 5-8 kg receive one pediatric tablet per day, those weighing 9-17 kg two pediatric tablets, those weighing 18-29 kg one adult tablet, and those weighing 30 kg and above two adult tablets.

c) IPT with a bimonthly course of treatment with sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ).

Amodiaquine plus sulfadoxine-pyrimethamine supervised at each bi-monthly clinic visit (amodiaquine 10mg/kg per day for three days and sulfadoxine-pyrimethamine (25/1.25 mg/kg) on the first day).

d) Environmental control:

- Indoor residual spraying of insecticide
- Use of mosquito netting across doors and windows
- Sleeping under long-lasting insecticide-treated bed net
- Limit man - mosquito contact when outdoors

7.2.2 Prevention of Anaemia:

Folate Supplement:

- Folic acid tablet: 2.5 – 5mg daily.

7.2.3 Prevention of Infections with Penicillins:

Prophylactic Oral Penicillin V

- Oral Penicillin from 2 months – 3 years 125mg bd > 3 years 250mg bd
- Penicillin prophylaxis should be given up to the age of 16 years
- If allergic to Penicillin, give Erythromycin at the same doses as Penicillin V.

7.2.4 Immunizations:

Covid 19 vaccine and Sickle Cell Disease

It has been established through a study that patients with covid 19 and sickle cell disease remain at a higher risk of hospitalization, development of pneumonia and pain compared to other individuals without sickle cell disease. although the case fatality rate of sickle cell disease and other individuals were not significantly different from those of other individuals without sickle cell disease.

It is recommended that all sickle cell disease patients are to take Covid 19 vaccines.

According to a recent (Saturday, June 18, 2022) recommendation by the CDC, children 6 months to 5 years of age can now be vaccinated with the Pfizer-BioNTech or Moderna vaccines to better protect them from COVID-19. All children, including children who have already had COVID-19, should get vaccinated.

Reference

Table 8: Immunization Schedule 1

Immunization	**When**
BCG	At birth
OPV_0	At birth
OPV_1	6 weeks
OPV_2	10 weeks
OPV_3	14 weeks
Hepatitis B_1	At birth
Hepatitis B_2	6 weeks
Hepatitis B_3	14 weeks
Haemophilus Influenza	3, 6, 10, 14 weeks
DPT	6, 10, 14 weeks
Pneumococcal Vaccine	Pneumococcal Conjugate13 Valent Vaccine from 6 weeks (monthly x 3 doses) and a booster at 12 months, followed by Pneumococcal Polysaccharide 23 Valent Vaccine from 2 years with a booster dose 3 years later
Measles	9 months
Yellow Fever	9 months

Note: ***In states where pentavalent vaccines (Hep B, Haemophilus Influenza, DPT) are used the schedule below should be adopted.***

Nigerian National Immunization Schedule for Children

MINIMUM AGE OF CHILD	TYPE OF VACCINE	BENEFITS TO CHILDREN
At birth	*BCG	Prevents tuberculosis including bloody cough and permanent brain damage
	**OPV0	Partially protects against poliomyelitis which causes paralysis and death.
	***Hep B birth	Partially protects against hepatitis B which causes blood infection, liver diseases, cancer and death.
6 weeks	Pentavalent (DPT, Hep B and Hib) 1	Partially Protects against 5 diseases - diphtheria, whooping cough, tetanus, hepatitis B and Influenza.
	Pnemococcal Conjugate Vaccine (PCV) 1	Partially protects against most causes of pneumonia and meningitis including blood and lung infections and brain damage
	OPV1	Partially protects against poliomyelitis which causes paralysis and death.
10 weeks of age	Pentavalent (DPT, Hep B and Hib) 2	Partially protects against 5 diseases - diphtheria, whooping cough, tetanus, hepatitis B and Influenza.
	Pnemococcal Conjugate Vaccine (PCV) 2	Partially protects against most causes of pneumonia and meningitis including blood and lung infections and brain damage
	OPV2	Partially protects against poliomyelitis which causes paralysis and death.
14 weeks of age	Pentavalent (DPT, Hep B and Hib) 3	Prevents 5 diseases - diphtheria, whooping cough, tetanus, hepatitis B and Influenza.
	Pnemococcal Conjugate Vaccine (PCV) 3	Prevents pneumonia and meningitis including blood and lung infections and brain damage
	OPV3	Prevents poliomyelitis which causes paralysis and death.
	IPV	Prevents poliomyelitis which causes paralysis and death.
6 months	Vitamin A Supplement	Protects against night blindness, improves child's vision and boosts child immunity against infectious diseases
9 months	Measles	Prevents measles which causes blindness, deafness, lowered immunity and death.
	Yellow Fever	Prevents yellow fever which causes liver diseases and death.

**BCG should be given preferably at birth (within 2 weeks) but can be given up to 11 months of age*
***OPV0 must be given before the age of two weeks*
****Hep B birth to be given within 24 hours after birth preferably, but can be given up to 14 days of birth*

Parents and health workers to
NOTE THAT ALL CHILDREN UNDER FIVE YEARS OF AGE MUST BE IMMUNIZED AGAINST POLIO during every immunization plus days (IPDs) and other supplemental immunization activities.

***BCG** = Bacillus Calmette Guerrin.*

***Pentavalent vaccine** = Diphteria, Pertussis, Tetanus, Hepatitis B, Haemophilus Influenza B Vaccine.*

***OPV** = Oral Polio Vaccine.*

***IPV** = Injection Polio Vaccine.*

7.2.5 Additional vaccinations for SCD:

Immunization	**When**
	Vaccine from 2 years with a booster dose 3 years later
Measles	9 months
Yellow Fever	9 months

7.3 Growth and Development Monitoring in children with Sickle Cell Disease

Growth and development in children with SCD need to be monitored by measuring the following:

a) Weight

b) Height

c) Mid-Upper Arm Circumference (MUAC): MUAC should be > 12.5cm from children 1-5 years. In children aged 1-5years, the Child MUAC tape is used to assess nutritional status. Severe acute malnutrition is shown red (less than 11.5cm), moderate acute malnutrition in yellow (11.5cm-less than 12.5cm) and normal nutrition is shown in green (greater than or equal to 12.5cm).

Note that the weight and height should be plotted on the growth chart. using Road-to-Health Chart in order to identify individuals that may have growth retardation.

7.4 Home Care in Sickle Cell Disease

7.4.1 Nutritional requirements for patients with SCD

Infants and Children (1-5 years):

The continuum of infant feeding from birth till 24 months is referred to as Infant and young Child Feeding (IYCF) practices. The global and national recommendation for optimum Infant feeding from birth to 24 months of age are as described below;

i. Early initiation of breastfeeding (EIB): Early initiation of breastfeeding is advised.

ii. Exclusive breastfeeding for 6 months should be encouraged.

iii. Appropriate and safe complementary feeding from 6 months and continued breastfeeding up to 2 years and beyond (WHO &UNICEF).

iv. Appropriate complementary feeding to ensure a balanced diet. (Referral to a nutrition expert may be required).

Put in a table in the annex

7.4.2 Recognition of Early Features of Crises in Sickle Cell Disease:

i. Caregivers should be taught how to recognize pallor (whiteness of the palms, soles of feet, skin, and lips) and checking the conjunctivae for yellowish discoloration and abdomen for splenic enlargement

ii. They should also be taught to properly assess the severity of pain and early signs of ill health such as listlessness, refusal to play and fever.

iii. Once the above signs are noted, parents/caregivers should seek prompt medical attention.

7.5 Recommended Regular Clinical Assessment of Sickle Cell Disease Patients in Steady-State at the Out-Patient Clinic

7.5.1 Every three to six (3-6) months

i. Assessment of pain using Wong-Baker Pain Rating scale during every visit in pediatric visit

ii. Take a good systematic review of the patient's

iii. Do thorough Physical examination and obtain vital signs

iv. Carry out Laboratory investigations such as:

- Complete/Full Blood Count

- Liver Function Tests (Total plasma protein with albumin globulin fraction)
- Urinalysis to detect albuminuria
- Kidney Function Test

7.5.2 Annually/Bi-annually

i. Echocardiography to detect pulmonary hypertension
ii. Ophthalmology review
iii. Dental review
iv. ENT review
v. Transcranial Doppler Ultrasonography to identify individuals at risk of stroke from 2-16 years.
vi. Refer for orthopaedic and pulmonology review from13 years of age.

7.5.3 Meeting

Regular patients support group/individual patient meetings with caregivers who provide various components of holistic care, such as counseling, information about sickle cell disease, must be encouraged by the healthcare worker/attending clinician etc.

CHAPTER 8

GENETIC COUNSELING AND TESTING IN SICKLE CELL DISEASE

8.1 Introduction

Sickle cell disease is an inherited blood disorder passed on to the offspring of people who are carriers.

Definition: Genetic Counseling is a non-directive art of providing accurate, full, and unbiased information in a caring relationship to an individual or family affected by a genetic disorder to enable them to come to terms with and cope better with the disorder.

Principles Of Genetic Counselling

- **Informative:** The genetic counselor must give accurate, full and unbiased information including correcting any myths, wrong or superstitious beliefs.
- **Supportive:** Empathize and support decisions taken by clients and also help clients explore their self, feelings, attitude, values and never be judgmental.
- **Non-Directive:** Give accurate information to guide decision-making but don't direct clients on what to do.
- **Confidential:** Confidentiality must be maintained to assure the client that their privacy is respected.

Note: Sickle cell patients are called clients by genetic counselors.

8.2 Counseling Process

The counselor should ensure basic understanding and ensure the following:

1. Counseling should be done by a certified Genetic Counsellor or a health care personnel certified in genetic counseling
2. Give a warm welcome to the patient and make the patient comfortable and introduce yourselves.
3. Ensure the sitting arrangement has facial contact with the client.
4. Avoid of factors that hinder counseling.
5. Obtain an accurate family history and diagnosis of the client's genotype and that the client is feeling well and comfortable and does not at that moment need medical attention.
6. Inform the client about the duration of the session
7. Be a good listener.
8. It is also important to use simple and clear terminology with the clients.
9. Establish prior knowledge and perception of the client about SCD

10. Tactfully dispel myths and misconceptions about SCD e.g Abiku and Ogbanje
11. Do not give too much information more than the clients can absorb.

8.3 Why Genetic Counseling and Testing in Sickle Cell Disease?

a) Genetic Counselling and Testing help to identify and provide accurate information to affected individuals and family members about the condition and how it is passed, verbally through inheritance pattern diagrams and educational materials.

b) Genetic counseling is important before any genetic test is carried out.

c) It is essential to tactfully but firmly dispel myths and misinformation held by the client, family members, and community about the disorder.

d) It ensures that the affected person understands the probable clinical course and treatment needs.

e) It provides an avenue for the clients to learn about standard health care facilities they should visit.

f) It informs the client about existing facilities for health and social care and provides a referral where necessary

g) It provides an avenue to educate clients about the inheritance of SCD

h) It provides the client with a spectrum of careers that are compatible with living with sickle cell disorder

i) It provides the opportunity to encourage affected clients and their family members by referring them to successful role models living with SCD.

j) It reduces stigmatization, low self-esteem, despair, and fears, which are replaced with confidence, hope, and a positive self-image.

k) It enables a better understanding of sickle cell disorder and better coping mechanisms.

l) It helps couples and prospective couples at risk to make informed decisions in respect of marriage, pregnancy, prenatal diagnosis, and preimplantation genetic diagnosis.

8.4 Challenges of Counselling in Sickle Cell Disease

Owing to a large number of people, groups, languages, and diverse terrain in the country, counseling can be challenging.

To ensure that clients understand the information presented to them, counseling should be done in local languages without losing the essential facts.

The challenges of genetic counselling in Nigeria include:

i. Language barrier I an interpreter may not be available

ii. Limited number of certified genetic counselors

iii. Financial constraints in producing Social and Behavioral Change Communication (SBCC) educational material.

CHAPTER 9

NEWBORN SCREENING AND DIAGNOSIS IN SICKLE CELL DISEASE

9.1 Introduction

According to the Nigeria's 2018 Demographic and Health Survey (NDHS) showed prevalence of HbAS (19·7%), HbAC (1·6%), HbSC (0·4%), HbSS (0·9%) of 11, 391 children aged 6–59 months compared to 1·4% for HbSS in a cohort of 3,603 new-born. In addition, the survey reported that 10% of the children aged 6 months to 5 years who were found to have severe anaemia were also shown to have Sickle Cell Anaemia (SCA). Estimates of child mortality from sickle cell disease between 2003 and 2013 with at least 1 younger sibling in the survey had about 370 excess under-5 mortality per 1,000 live births than children with HbAA.

World Health Organization (WHO) reported that an estimated 150,000 babies are born annually in Nigeria with SCD. This is projected to increase to 450,000 by 2050 if nothing is done without intervention. This is a large number requiring huge resources for diagnosis and comprehensive care which consequently constitutes a drain of scarce family resources.

Newborn Screening (NBS) is carried out at birth or at the neonatal period to enhance early detection of sickle haemoglobin. Experiences from developed countries have shown significant reduction in mortality and morbidity in individuals affected by SCD when they are identified at birth and evidence-based interventions are applied (e.g education, genetic counselling, prophylaxis for infections, prevention and screening for stroke, Hydroxyurea therapy, monitoring and early treatment of complications etc) in a comprehensive care program, . [12],[13],[14].

9.2 Component of a newborn screening program

NBS program should be anchored in the public health system integrated into existing maternal and childcare and early infant diagnosis of HIV programmes. A NBS program comprises Screening, Diagnosis, Education, Treatment and comprehensive care according to the NCD policy.

9.3 Requirements of a NBS Program

For a successful NBS program, the following factors needs to be fully worked out:

1. Sites/location for sample collection: primary health care centers and other health care facilities, home, traditional birth attendance (TBA) center, immunization clinic.
2. When the samples will be collected:
   - At birth or soon after
   - At postnatal clinics usually at 2 weeks and 6 weeks
   - At first immunizations (6wks - 14 weeks), measles at 9months.
3. Screening Laboratory: Tests to be used for screening and confirmation •
4. What happens to the results
5. Person responsible for parental follow-up and scheduling clinical visit.
6. When/Where the confirmatory testing should be conducted
7. Clinical Network for follow up and care of screening detected babies

8. Drugs and Immunizations
9. Data Management:
    - Sickle Cell Disease registry integrated into NHMIS (National Health Management Information System

9.4 Sites/location for sample collection

Facilities where newborn screening and sample collection should be carried out include primary health care centers and other health care facilities (secondary, tertiary, private clinics, hospitals) home, traditional birth attendance (TBA) homes, immunization clinic.

9.5 When should samples be collected

Sample should be collected from the newborn at birth or soon after, at postnatal clinics usually at 2 weeks and 6 weeks, at first immunizations (6wks - 14 weeks), measles at 9months after parental counselling and informed consent.

Sample will be collected from a heel or finger prick for testing using validated simple, reliable, effective and low-cost Point of care test/screening devices (POCT).

9.6 Steps in Collection of Sample

Materials:

a) Point of care test kit for screening for SCD

b) Disposable gloves

c) Sterile lancets

d) Methylated spirit swabs

e) A register with baby's name, DOB, gender; parents' names as known in the community, occupation, house address with nearest landmarks, phone numbers and relative/neighbors phone number etc, Parent's genotype if known).

f) A form to issue screen results with the same details as in the register.

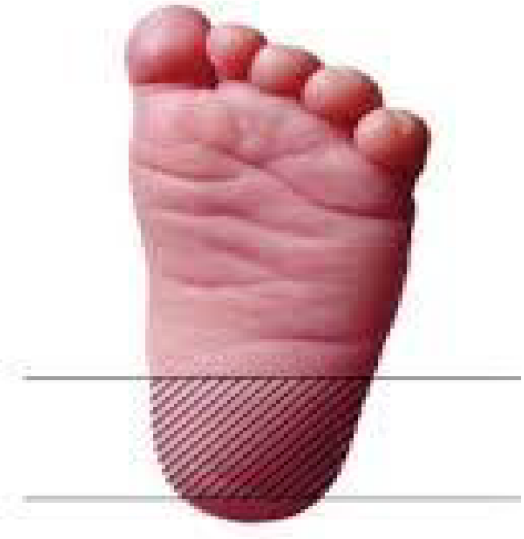
Procedure:

a) Obtain verbal consent from the mother/caregiver

b) Sample is collected through heel prick by the birth attendant/designated health worker as soon as possible after birth. The heel of the newborn baby is gently massaged, and side of the heel is pricked with a disposable sterile lancet applying aseptic technique. The posterior aspect of the heel should be avoided as shown:

For term and preterm infants

For older infants and those who have had repeated pricks



c) Obtain sufficient blood sample required for

d) Apply dry swab to the pricked area to stop the bleeding

e) Follow manufacturer instructions for the use of the POCT kit

f) Counsel mother/caregiver and issue test result.

g) Babies who tested HbS screened positive, collect dry blood spot (DBS) samples with another heel prick for confirmatory test by HPLC/IEF at the reference laboratory.

h) See the HbS screened positive babies at 6 weeks immunization date with confirmatory test result.

i) For confirmed sickle cell trait (HbAS)- give further counselling

j) For confirmed Sickle cell disease (HbSS, HbSC and others) – give further counselling and register for follow up care at the PHC/nearest PHC and also link to a comprehensive SCD care center at a secondary or tertiary level facility.

9.7 Collection and Transportation of DBS Samples for confirmatory test.

Collection of DBS samples will be done at same maternity units/screening sites from HbS screen positive babies immediately after obtaining result of screening with the POCT kit.

Materials:

a. Disposable gloves

b. Sterile lancets

c. Methylated spirit swabs

d. Dry blood spot (DBS) cards (labelled with Baby's name, date of birth, sex; parents' contact address and phone number, unique code)

e. A register (baby's name, DOB, gender; parents' names, occupation, contact address, phone number etc).

Procedure:

a. Obtain verbal consent

b. Sample is collected through a heel prick as performed for the initial screening as soon as possible after obtaining result of the POCT. The heel of the newborn baby is gently massaged, and side of the heel is pricked with a disposable sterile lancet applying aseptic technique as described above.

c. Put the blood on all the spots on the absorbent spots on DBS card/absorbent paper.

d. Apply dry swab to the pricked area to stop the bleeding

e. Allow the card to dry and stack at the appropriate place (cool and dry).

f. Send samples to reference laboratory equipped with NBS machine (HPLC/IEF) for analysis as soon as possible

g. The following information are required on a form that accompanies the DBS card/absorbent paper (screening intake form, see appendix):

- Baby's age (to be captured on a separate sheet)
- Baby's name and DOB on the absorbent paper
- Baby's gender
- Single or multiple gestation
- Date of sample collection
- Mother's/father's name as known in the community
- Contact/mobile number of parent and important landmark
- Parents' genotype if known.
- Sample site
- Name and ID of sample collector

Next Step:

i. The collected samples (DBS cards) are moved by a designated person in waterproof/tight package (e.g Ziplock bag) from the sample collection site to the reference laboratory within a week using standard operating protocol.

ii. In each screening site, one trusted and trained worker should be dedicated to receiving results electronically. The screening result will be released by the reference laboratory in the format attached (see appendix). The screening result will also be sent to the comprehensive center for SCD where a registry linked to the National Sickle cell disease registry will be maintained.

Note:

- ***Every mother should be asked about NBS at post-natal clinic or during immunization***
- ***If it is discovered that a child did not have NBS, the mother should be advised to have the child screened***

This approach will help capture, as much as possible, children that were delivered at home.

12.1Laboratory Confirmatory Testing of Newborn Blood Samples

High performance liquid chromatography (HPLC) systems or Isoelectric focusing (IEF) system shall be used for the confirmatory test at the reference laboratories using standard operating protocols by trained laboratory personnel.

12.2Communicating and Release of Confirmatory Result

Communicating the results to the parents/caregivers is an important aspect of the screening process which should be handled carefully as it is associated with a lot of sentiments (including rejection, depression, aggressiveness, stigmatization and family break up). The purpose is to reveal the newborn screening results and address the concerns of the parents. Results should be communicated to the parents by certified genetic counsellor or designated personnel trained in genetic counseling.

Steps in Communicating the Result (refer to the genetic counselling section pg xxx):

12.2.1.1 Reveal the results and discuss the implications of the result with the parents

12.2.1.2 Observe reactions to the result

12.2.1.3 Counsel and address concerns/myths and questions of the family

12.2.1.4 Provide psychological Support

12.2.1.5 Educate and provide social and behavioral change communication (SBCC) materials

Counselling (Refer to section on genetic counselling for details)

a) Explain what SCD is
b) The Traits and how it combines to give SCD
c) Health problem that could occur in SCD
d) Medical management and options
e) Enrolment into comprehensive care as described in this document for positive cases at a dedicated SCD centres
f) Educate and provide educational materials addressing danger signs such as fever, persistent headache, abdominal pain, priapism, vomiting and diarrhoea, features of severe anaemia and chest pain with breathlessness.

Note: ***Revealing the results of genetic screening should only be done by a certified genetic counselor.***

Care at the Primary Health Care Facility

i. Babies screened and identified at facilities other than the PHC screening sites should be referred to the nearest primary health center (PHC) for primary care of SCD.
iii. All babies identified with SCD must be registered and seen regularly at the nearest PHC using the protocol attached (Primary level care for SCD- appendix xxx)

Linkage to Comprehensive Care Programme for SCD

1. All babies identified through the screening program must be linked from the PHC to the nearest secondary or tertiary level facility offering comprehensive care for SCD.
2. *Comprehensive care should be offered using the National Guideline for the control and management of SCD.*

12.3Data Management

12.3.1 Objectives

A national registry of newborn with SCD (NRNSCD) should be established with the following objectives:

12.3.1.1 For prospective surveillance
12.3.1.2 For data collection for decision making and planning of intervention

12.3.2 Plan

12.3.2.1 Start maintenance of the NRNSCD at all existing/available SCD center that offers comprehensive care for SCD.
12.3.2.2 Data to be captured in the database shall include:

- DOB
- Age at screening
- Sex
- Baby‟s name
- Mother‟s name
- Place of delivery
  - State
  - LGA
  - Political ward
- Centre of registration
- Hospital number
- Current address
  - State of Origin
  - Local Government Area
  - Political ward
- Contact telephone (Father, Mother)
- Baby‟s weight

- NHIS number if available
- Birth order
- Results of SCD screening
- Identification of other babies in the family with SCD
- Type of sample taken
- Rank of birth
- Centre to input into FMOH website on Research & Statistics
- Need for software to manage the information input
- Input of data into the system by Health Information Officer in the centre
- Data manager at the NCD Control Programme to inter-phase with the FMOH website on Research & Statistics.

12.3.3 Information to be put on the form for screening shall include:

12.3.3.1 DOB
12.3.3.2 Age at screening
12.3.3.3 Sex
12.3.3.4 Baby‟s name
12.3.3.5 Mother‟s name
12.3.3.6 Place of delivery
- State
- LGA

12.3.3.7 Centre of registration
12.3.3.8 Hospital number
12.3.3.9 Current Address
12.3.3.10 Contact phone number
12.3.3.11 State of Origin
12.3.3.12 Parents‟ genotype if known.

12.4Coverage of Newborn Screening

The success of NBS depends on adequate coverage backed up by legislation therefore the NBS program will be universal and must include strategies for early interventions

For this to happen, babies born in health facilities as well as those born at home shall be screened and linked to comprehensive care.

All stakeholders should be responsible for sensitization, advocacy and community mobilization for NBS. Babies born at home are best captured at immunization centers.

CHAPTER 10

10.1 CURATIVE AND NOVEL THERAPIES FOR SCD

Currently, Red Blood Cell (RBC) transfusion and Hydroxyurea are the major disease-modifying therapies available for SCD. While hematopoietic stem cell transplant is curative without changing the genetic status of the patient, barriers to treatment are substantial. Other curative therapies are still being developed in various clinical trials across the world.

Deeper insights into the pathophysiology of SCD have led to the development of novel agents that target cellular adhesion, inflammation, oxidant injury, platelets and/or coagulation, vascular tone, pyruvate kinase activation and haemoglobin polymerization.

These agents are in preclinical and clinical trials, and some have been approved by the FDA for clinical use.

Pathobiology Targeted	**Mechanism of Action**	**Therapy**	**Examples**	**Status**
Changing the phenotype	Modify Phenotype	Allogeneic HSCT	HLA-matched transplant Haplo-identical HSCT	Approved
	Modify Genotype	Autologous HSCT*	**Gene therapy**: - Gamma globin gene transfer - Lentoglobin bb305 - Lentivirus shRNA Lting BCL11A **Gene editing:** CRISPR Cas9 techniques	Clinical Trial. Clinical Trial.
Hb S polymerization	Increasing Oxygen Affinity	Voxelotor LBH589/Panobinostat (NCT01245179)	Voxelotor	FDA approved
Vaso-occlusion	P-Selectin inhibition	1. Crizanlizumab 2. Inclaclumab	1. Crizanlizumab 2. Inclaclumab	FDA approved Clinical Trial
	Increase NAD and NADH and reduce adhesion	L-Glutamine	L-Glutamine	Approved
Hb F induction	DNA methyltransferase 1 (DNMT1) inhibition	Decitabine		In clinical trials

r Voxelotor/GBT440 (NCT03036813) (FDA approved) α-Globin reversible binding Decitabine/THU (NCT01685515) DNMT1 inhibition Sanguinate (NCT02411708) Targeting carbon monoxide delivery IMR- 687 (NCT04053803) Phosphodiesterase 9 inhibitor

ALLOGENEIC Hematopoietic Stem Cell Transplant (HSCT)

Hematopoietic Stem Cell Transplantation (HSCT) was first reported about 40 years ago for SCD. An 8-year-old child with HbSS who had frequent VOCs, subsequently developed acute myeloid leukemia. She had HSCT for the acute myeloid leukemia from an HLA-matched **sister (HbAS), and was cured** of both her leukemia and her sickle cell complications. The procedure was first carried out in Nigeria, at the University of Benin Teaching Hospital on a 9year old boy with Hb SS in 2011. This was a success and several others have since been carried out.

Now it is an important therapeutic (curative) option for patients with SCD. More importantly, it can stabilize/restore function in affected organs of patients with SCD when performed in time.

HSCT establishes donor-derived erythropoiesis. Donors could be HbAA or HbAS and in order to reverse the sickle genotype, the myeloid donor chimerism has to be >20%.

The procedure of HSCT is associated with a 93% overall survival. However, when the patient is aged greater than 16 years, there is a worse overall survival (95% vs. 81%), and a higher probability of graft versus host disease (GVHD)-free survival (77% vs.86%).

Note: Physicians should provide early referrals to SCD patients for transplant evaluation so that the HSCT can be carried out in a timely manner.

Indications for Allogeneic HSCT in SCD

Allogeneic HSCT Donor Sources:

- Matched Sibling Donor
- Haplo-identical family members.
- Matched Unrelated Donor
- Unrelated umbilical cord blood (UCB)

Note: Unrelated umbilical cord blood (UCB) and haplo-identical HSCT - donor graft rejection remains a major obstacle in the context of Reduced Intensity Conditioning (RIC)

Conditioning Regimen

Conditioning regimens prepare the host bone marrow to receive the donor stem cells. These include the following:

1. Myeloablative conditioning (MAC) total body irradiation and an alkylating agent, usually Busulphan at doses that does not allow ic recovery
2. Reduced intensity conditioning (RIC) - (Fludarabine, alemtuzumab, melphalan)
3. Non-myeloablative conditioning (NMA) -, alemtuzumab, low dose total body irradiation and sirolimus in patients who have some degree of cumulative organ damage.

Note: The ideal conditioning regimen should provide adequate immunosuppression without rejection and minimal GVHD. RIC is the recommended modality for transplant in SCD. The toxicities associated with MAC cannot be readily supported in our environment.

Challenges of Allogeneic HSCT:

- Donor availability
- Transplant related mortality
- Need for immunomodulators to prevent GVHD
- Graft rejection
- Cost of the procedure

Autologous Hematopoietic Stem Cell Transplant Modification:

A. Gene Therapy & Gene Editing

Genetically engineered autologous cells eliminate the need to find a HSCT donor and thus available to all patients. Since these are the patient's own stem cells, there is no need for immunosuppression, thus eliminating the risks of GVHD and immune-mediated graft rejection.

The genetic defect in the sickle HSPCs can be corrected via several approaches:

i. Gene addition using lentiviral vector-based strategies
ii. Gene editing

B. Gene addition using lentiviral vector-based strategies

a. Anti- or non-sickling strategy:

Patient's stem cells are infected with a lentivirus expressing an anti-sickling β-globin variant, T87Q. The first SCD patient who received this was reported in 2017; engraftment was stable with no sickle cell crises reported at 15 months of follow up.

b. HbF induction strategy:

The well-established efficacy of increasing HbF has motivated both pharmacological and genetic approaches to HbF induction. One of the functions of the BCL11A gene is to turn off the production of Hb F, which usually occurs at about six months of age.

A gene addition approach in clinical trials uses a lentiviral mediated erythroid specific short hairpin RNA (shRNA) to target the BCL11A gene and downregulate its expression thereby inducing Hb F production (Brendel et al., 2016).

As at December 2018, three adults have been enrolled, all three patients showed prompt neutrophil engraftment and at 2 months follow up, the average HbF was 30% (ASH abstract #1023 – 2018 ASH conference).

Viral vectors, such as lentivirus are a great tool for gene therapy but these results underscore the need to develop gene transfer protocols that ensure efficient and consistent delivery of the therapeutic globin gene cargo to HSC.

Their major limitations include:

- Their immunogenicity can create an inflammatory response in the donor which can lead to degeneration of the transducted tissue.
- They can produce non-specific toxins
- Due to the semi-random integration to the genome, there is a theoretical risk of insertional mutagenesis,

- They have limitations of transgenic capacity size.

Gene Editing

Gene-editing corrects a specific defective DNA in its native location. SCD with its simple single base change presents a very attractive prototype for this technique.

Strategies have been developed that could precisely genetically correct a single base mutation in patients with SCD.

These strategies include:

1. Zinger Finger Nucleases (ZFN),
2. Transcription activator-like effector nucleases (TALENs)
3. The clustered regularly interspaced short palindromic repeat (CRISPR)-associated nuclease Cas9 approach which is the most advanced of the three.

These strategies are currently being tested in a clinical trials.

10.2 NOVEL THERAPIES

A. **Targeting HbS Polymerization:** Approaches targeting HbS polymerization presents a very attractive strategy.

Strategies:

i. **HbF induction using Hydoxyurea (HU**):

The use of HU has been extensively discussed in chapter xxxx

ii. **Anti-Sickling agent:** Voxelotor (FDA approved 2019)

Voxelotor is a small molecule that binds specifically to the N-terminus of the alpha subunit of HbS, increasing the oxygen affinity of the HbS to stabilize the oxygenated haemoglobin state thereby reducing its predisposition to sickling. The HOPE study showed an increase in haemoglobin levels and reduced markers of haemolysis in 274 patients with HbS that were randomly assigned to receive the study drug versus placebo.

B. **Prevention of Adhesion:**

Adhesion of platelets to red cells, monocytes, and neutrophils is an integral component of the pathogenesis of sickle cell disease. The degree of red cell adhesion correlates with the severity of the disease.

Selectins, especially P-selectin, is upregulated in sickle cell disease and is responsible for initiation of the static adhesion of the sickle red cells to the vessel surface and the ensuing vascular obstruction that is seen in VOC.

i. Crizanlizumab

Crizanlizumab is a monoclonal antibody to P-selectin. It blocks the adhesion of activated erythrocytes, neutrophils and platelets.

In a phase 2, multicenter, randomized and placebo controlled double blind study, crizanlizumab with or without hydroxyurea showed that patients on the treatment arm had significantly lower

rate of sickle-related pain crises compared to placebo with a lower incidence of adverse events. It is given intravenously every 4 weeks to reduce VOC. Others agents targeting adhesiveness are still in clinical trial

C. **Prevention of Oxidative Stress:**

L-GLUTAMINE

Studies had demonstrated that glutamine depletion contributed to red blood cell membrane damage and adhesion. In a phase 3 study, L-glutamine demonstrated a 25% reduction in the median number of pain crisis, 30% less hospitalizations and reduced acute chest episodes in children and adults with SCD with or without HU over a 48-week period. L-Glutamine appears to significantly increase NADH and NAD redox potential and decrease endothelial adhesion. The utilization and uptake is still low, it also has an unpleasant taste. There are concerns regarding its use in patients with renal impairment.

Phytomedicines

Phytomedicines are defined as medicines that are derived from plants in their original state, which have therapeutic properties. These are traditional herbal medicines, native to the part of the world where they are often used. They encompass many of the plant remedies from traditional healers which people with SCD would use.

Traditional medicines (including phytomedicines) are easily available, accessible, and culturally acceptable. They are often used by up to 80% of families affected by SCD in low- and middle-income (LMIC) countries, especially for painful episodes and other complications. This is especially so in sub-Saharan Africa including Nigeria, India and other LMIC of the world, with the greatest burden of disease, but limited healthcare services. Research has shown numerous potentially therapeutic agents with benefits for people with SCD. However, their use in SCD in these resource limited areas is not usually recommended by orthodox medical healthcare practitioners due to inadequate scientific knowledge of it.

Examples of these phytomedicines include:

1. **Niprisan®** (also known as Nicosan®), a freeze-dried extract of *Piper guineenses* seeds,

Pterocarpus osun stem, *Eugenia caryophyllu*m fruit and *Sorghum bicolor* leaves. Niprisan, a drug developed at the Nigeria Institute for Pharmaceutical Research, idu Abuja has been quite extensively investigated

2. **Ciklavit®** (*Cajanus cajan* seed extract as base and
3. ***Zanthoxylum (Fagara) zanthyloides*** are both locally available in Nigeria, and investigated at the Lagos University Teaching Hospital, Lagos, Nigeria
4. ***Pfaffia paniculata*** - a drug researched in india
5. **EvenFlo®** - a drug used in a randomized double blind clinical trial in Kenya with promising result in crisis reduction and improvement in boosting hemoglobin concentration and weight in SCD patients.

Research both in vivo and in vitro has shown beneficial effects of these phytomedicines in SCD. These effects include:

1. Delay of polymerisation of haemoglobin S, as well as reversal of sickling of red blood cells when exposed to low oxygen tension by Niprisan and Ciklavit
2. Increase Hb F production by *broccoli sprout homogenate*, *labdane diterpene*, *Curcuma comosa*

and *Pfaffia paniculata.*

3. Improvement of deformability and hydration of red blood cells by *Pfaffia paniculata*, *Raphiostylis beninensis* stems and *Lonchocarpus cyanescens*
4. Inhibition of haemolysis of red blood cells
5. Increase oxygen affinity of Hb S by *Monodora myristica*

A 2020 Cochrane systematic review of phytomedicines in use for SCD has evaluated the effect of these medicines. Three randomized controlled trials with 212 participants; and three phytomedicines Niprisan® (also known as Nicosan®), Ciklavit® both from Nigeria, and the powdered root extract of *Pfaffia paniculata* from India were included. Results showed Niprisan® may reduce episodes of sickle cell disease crises associated with severe pain, while Ciklavit® may have little effect in reducing these painful crises, and a possible adverse effect on the level of anaemia. The other phytomedicines showed no serious adverse events.

More scientifically robust trials of these medicines will need to be carried out before recommendations about their use can be made. The results of the Phase III clinical trial for Niprisan® is still being awaited. Further research should also assess long-term outcome measures.

CHAPTER 11

PSYCHO SOCIAL SUPPORT (PSS) AND NON-PHARMACOLOGICAL APPROACH IN THE MANAGEMENT OF SICKLE CELL DISEASE

Introduction

Sickle cell disease (SCD) is a biopsychosocial disease (Omoigui). It is the most prevalent inherited blood disease in the World (Stephen et al., 2018). It is the most common genetic disorder amongst Black people, poses a significant psychosocial burden on the sufferers, the caregivers, and their families (Adegoke, Kuteyi, & Medicine, 2012). It is a chronic, hereditary, and congenital blood disorder affecting SCD up to 100 million people worldwide, predominantly amongst Black people in Africa, Europe and the America, Arabian people, and those of Asian ancestry (Adegoke et al., 2012).

In Nigeria, it is estimated that about 150 000 children are born with sickle cell anaemia annually, with a prevalence of 20–30 per 1000 live births whilst that of haemoglobin SC is approximately 0.7% (Organisation, 2006).

The impact of SCD on the family is worse in developing countries such as Nigeria because of inadequate social welfare and health care services. It is, therefore, a potentially serious clinical and public health problem that merits the attention of psychologists working in medical settings.

Despite its prevalence. psychological complications in patients with SCD are common. In addition to experiencing myriad medical problems, patients with SCD often manifest neurocognitive impairments and learning problems, internalising, and externalising of behaviour problems, problematic interpersonal relationships, low self-esteem, maladaptive coping strategies, reduced health-related quality of life because of negative mood, and daily activity and role limitations (National Academies of Sciences & Medicine, 2020).

Generally, the overall health of these patients has been dependent on the quality of life and psychological preparedness of the caregivers. However, treatment advances over a generation have greatly improved the quality of life and longevity of patients.

Clinicians need to learn more about the way SCD patients adapt to their condition. This can be achieved through combining medical treatment with investigations that assess daily psychosocial experience, and the long-term effects of both medical and psychological therapies.

Psychosocial management of sickle cell disease and its associated pain is an increasing challenge to both clinicians and patients. In the absence of a universal cure, it is recommended that psychological interventions should be incorporated into protocols for the management of patients with SCD and offered as standard care to help improve their general quality of life within a multidisciplinary context.

This evidence-based policy guidelines is hereby designed for the psycho-social support (PSS) and non-pharmacological approach (NPA) to the management of sickle cell disease (SCD)-related acute and chronic pain in children and adults.

Rationale for the Policy Guidelines

Three subtypes of chronic pain have been identified in SCD:

- chronic pain without contributing SCD complications, such as leg ulcers or AVN
- chronic pain with contributing SCD complications

- mixed presentation, when there is evidence of chronic pain from SCD complications but also apparently unrelated persistent pain

Severe pain is the most common complication of SCD and affects individuals' quality of life. Acute pain episodes are the leading cause of emergency department visits and hospitalizations for individuals living with SCD. Further, chronic pain develops as individuals age and affects them daily.

Acute and chronic pain management is a common clinical challenge for health care providers. This is in part due to the lack of strong evidence to support clinical decision-making.

Health care providers may be unaware of all the available tools that can be used to manage acute and chronic SCD pain. These tools include both medications and treatments that are not medications

Who will use this guidelines?

- Haematologists and other clinicians providing pain management care
- Emergency room physicians
- Primary Care and Family Physicians
- Individuals living with SCD and their family members
- Policymakers

Scope

- SCD Pain
- **Opioids Use and Substance Abuse**: Substance use disorders are to be covered by this policy insofar as there is comorbidity with SCD painful crises

Categories of People Benefiting from Psycho-social support and Non-Pharmacological

1. Affected individuals
    a) **Children with sickle cell anaemia (SCA)**: Children with SCD often exhibit fewer behavioural problems and less maladjustment than adolescents with SCD
    b) **Adolescents with sickle cell anaemia (SCA)**: Adolescent boys have more frequent behavioural and social adjustment problems than adolescent girls
    c) Patients transitioning from adolescence to young adulthood
    d) Adults with sickle cell disease ages over 18 years
2. SCD-at-Risk Couples
3. Pregnant women
4. Women identified as high risk through antenatal tests
5. Family/Caregiver of persons with genotype SS or AS and other variants

Psychosocial Problems of Patients with Sickle Cell Anaemia

Vulnerabilities of Patients with SCD

Globally, children, adolescents, young adults with SCD are at increased risk of mental health and psychosocial issues.

Some of the common psychological complications found across the life span of patients with sickle cell disease (SCD), which are likely to be encountered by mental health professionals and haematologists responsible for their medical management include:

1. **Psychological coping**

    a) **Psychological Distress:** Mood is a component of SCD pain experience, related quality of life and medication use (Anie & Steptoe, 2003). These include increased anxiety, depression, social withdrawal, aggression, poor relationships and low self-esteem. Anxiety and depression are psychological complications of SCD with important consequences. Patients with SCD commonly report low self-esteem and feelings of hopelessness as a result of frequent pain, hospitalizations and loss of schooling (in children) and employment (in adults). These accounts could indicate depressive symptoms and should not be ignored in clinical practice.

    b) **Psychosocial Impairments**: SCD is a serious life-threatening illness that increases the risk of adjustment problems in patients. These include:

        i. Social Adjustment Problem: These implies problems related to social and academic/vocational functioning

        ii. Emotional Adjustment Problems in the form of internalising symptoms such as anxiety and depression

        iii. Academic Adjustment Problems

        iv. Family Adjustment Problems

        v. poor school performance

2. **Medication Use for SCD:**

    a) Problematic adherence to medical regimens:

    b) SCD patients, sometimes referred to as ‘problem patients’, usually demand very high doses of opioids.

    c) **Psychologically dependent on opioids and Drug Abuse**: Drug overdose is one of the major cause of non-medical death among SCD patients (Ruta & Ballas, 2016)

    d)

3. **Quality of life:** This entails the following problems:

    a) **Activity and functioning:** Impaired psychological well-being, limitations in social activity, work and domestic roles

    b) Inappropriate pain coping strategies.

    c) Reduced health-related quality of life in adults with SCD owing to restrictions in daily functioning, anxiety and depression.

4. **Neuropsychology Complications:**

a) Cerebrovascular disease, particularly ischaemic brain injury or stroke is the most disabling complication in SCD, with younger children generally developing infarcts while older patients are more inclined to haemorrhage (Powars, 2000).

b) Cerebrovascular accidents are related to SCD severity, hypoxaemia, silent cerebral infarcts and neurocognitive impairment/deterioration and intellectual impairment in children

c) The SCD children with overt strokes usually have neuropsychological complications that have been shown to relate to the location and size of the lesion in the brain.

d) Language and verbal problems are associated with the left hemisphere, visual/motor deficits are related with the right hemisphere, while attention and executive function are linked to the frontal lobe.

Psychosocial Vulnerabilities of SCD Affected Families

a) High levels of parental anxiety

b) Overprotection

c) Excessive feelings of responsibility and guilt

Causes of Psychosocial Problems of Patients with Sickle Cell Anaemia

Various personal, social and environmental factors influence the wellbeing of SCD patients and families and their ability to recover from pain crises.

Psychological complications in patients with SCD mainly result from the following (Oluwatoyin Olatundun Ilesanmi, 2010; Oluwatoyin Olatundun Ilesanmi, 2013; Oluwatoyin Olatundun Ilesanmi, 2014):

a) frequency of serious pain episodes

b) impact of pain and symptoms on their daily lives

c) society's attitudes towards patients with SCD

d) increase in health care utilisation.

Conceptualization of PSS and NPA interventions for SCDs Pain Management

Psychological therapies and non-pharmacological pain management are the management of pain without medications. This method utilises ways to alter thoughts and focus concentration to better manage and reduce pain.

Evidence-based nonpharmacologic therapies are safe and effective components in comprehensive pain care that can also be opioid sparing, that is, reduce the need for opioids to manage severe, acute pain and consequently reduce the need for chronic opioids.

Nonpharmacologic therapies can be stand-alone interventions or work in combination with medicine, procedures or surgery. An often underrecognized feature of nonpharmacologic therapies is their ability to confer additional benefits: a treatment to reduce pain can also reduce anxiety and depression, nausea and vomiting; facilitate restful sleep; and increase a patient’s sense of well-being and desire to participate in their own recovery.

Some of the psychological therapies and non-pharmacological alternatives most commonly used by persons with SCD to treat pain include cognitive behavioural therapy, biofeedback, prayer, relaxation techniques, acupuncture, hypnosis, herbal therapies, megavitamins, community support groups, exercise, and other approaches.

Lifestyle or behavioural approaches, such as stress management, cognitive behavioural therapy, meditation/mindfulness and meditative movement therapies are also recommended as nonpharmacologic strategies. Other lifestyle approaches

including diet and sleep hygiene have been shown to benefit health. These are low risk, low cost, well accepted by patients and many have been used successfully for thousands of years.

These therapies are also known as complementary and alternative therapies. They may be delivered by

a) Licensed and regulated professionals - such as acupuncture therapy, massage therapy, osteopathic manual medicine, chiropractic, physical therapy and psychology.

b) Instructors trained in evidence-based, directed or self-engaged movement and meditative movement therapies as in yoga and Tai chi.

Values	Principles
PSS and NPA are parts of general pain management for SCD patients	➢ PSS and NPA should be integrated into general health care ➢ PSS and NPA should be planned at all levels of the health service ➢ The well-being of all SCD patients depends upon the interplay of physical, social, cognitive, emotional, and spiritual elements. ➢ PSS and NPA have a critical role in creating and supporting conditions for SCD patients and their families' optimal development and wellbeing.
Human rights	➢ The rights to equality, non-discrimination, dignity, respect, privacy, autonomy, information and participation should be upheld in the provision of PSS and NPA services to SCD patients and their caregivers
Community Care	➢ Local community-based resources should be mobilised wherever possible. ➢ A recovery model, with an emphasis on PSS and NPA should underpin all community-based services
Gender	➢ Services should be sensitive to gender-related issues experienced by men and women, and boys and girls.
Efficiency and effectiveness	➢ All persons with SCD and their caregivers have assets or resources that support their mental health and psychosocial well-being ➢ Interventions should be informed by evidence of effectiveness.
Protection against vulnerability	➢ Vulnerabilities to psychosocial problems and opioids abuse associated with pain crises in SCDs should be protected against through the provision of targeted prevention interventions.
Social support and integration	➢ Maximum support should be provided to families and carers of those with SCDs, to broaden the network of support and care. ➢ Engagement and participation of families, caregivers, and communities and SCD patients themselves is central to ensuring enabling environments for children's development and securing their protection, wellbeing and future potential.

International and Local Legal Frameworks for Psycho-social support (PSS) and Non-Pharmacological Approach (NPA)

PSS and NPA are critical component and fundamental parts of pain management as stipulated in the following international treaties to which Nigeria is signatory:

a) United Nations Global Strategy for Women's, Children's and Adolescents' Health for 2016-2030;

b) UNICEF's Core Commitments for Children (CCC) in Humanitarian Action, released in 1998 and revised in 2010

c) The UN General Assembly's Convention on the Rights of the Child

d) The IASC Guidelines on MHPSS in Emergency Settings (2007)

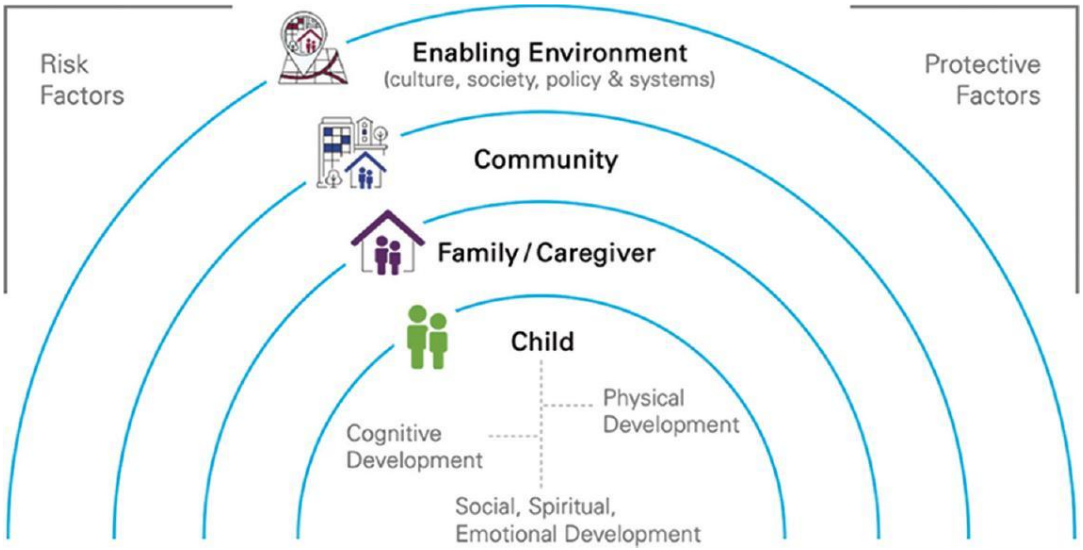
e)

Values and Principles Standards Underpinning This PSS and NPA Guidelines for Pain Management

Models of Care

a) **Health Belief Model**: This framework guides understanding about how psychosocial variables influence SCD patients' health care utilisation.

b) **Social Ecological Mode**l: The social ecological model illustrates the importance of networks of people and structures that surround the SCD patients, safeguarding their well-being and supporting their optimal development. Based on this model, the SCD patients is at the centre nested within concentric circles consisting of family, community, and culture/ society



c) **Theory of Change**:

With pain management, there are multiple drivers for SCD patients' vulnerability and resilience. Patients and families may define their needs and priorities differently in each crisis event. The theory of change explains how mental health and psychosocial support interventions directed at the SCD patients, the family/caregiver and the community can help to reduce suffering and improve people's mental health and psychosocial wellbeing.

The theory of change includes strategic actions and considers causes of the problems affecting SCD patients' safety and wellbeing. It also addresses barriers in crises situations that may influence PSS and NPA programme design, implementation and outcomes.

<table>
<tr><td colspan="6">Theory of Change for PSS and NPA</td></tr>
<tr><td>Problem</td><td>SCD erode family and community structures and supports for patients' mental health and psychosocial Well-being and safety</td><td>Goal:</td><td>Reduced suffering and improved mental health and psychosocial wellbeing of children and families.</td><td>Causes:</td><td>Genotype SS and other variants

Episodic Painful Crises</td></tr>
<tr><td colspan="6">OUTCOMES</td></tr>
<tr><td colspan="6">a) Reducing of pain
b) Preventing drug dependence and self-harm harm
c) Strengthening resilience to recover from painful crises
d) Improving the care conditions that enable patients and families to survive and thrive</td></tr>
<tr><td colspan="2">Patients</td><td colspan="2">Family/Caregiver</td><td colspan="2">Community</td></tr>
<tr><td colspan="2">● Safe, nurturing environments: Safe spaces, safe and supportive school environments, support to vulnerable families and violence reduction
● Positive relationships:
Sibling-to-sibling, Peer-to-peer for patients with SCD and MNS;
Cultural and expressive activities for patients and their families/caregivers
● Stimulation, learning, skills development:
ECD activities,
building teacher capacities in SEL,
vocational training for adolescents with SCD and MNS</td><td colspan="2">● Focused care for distressed caregivers,
● Specialised PSS and NPA care for SCD and MNS patients with MNS disorders,
● Psychosocial Support in coping for parents and teachers
● Awareness-raising of distress reactions
● promotion of positive parenting knowledge and skills, support for parents/caregivers in caring for SCD patients with MNS disorders
● Caregiver/women's/men's support groups, facilitation for inclusion and participation of vulnerable families in communal activities</td><td colspan="2">● Wellbeing And Protection Awareness-Raising: Stigma reduction campaigns for people with MNS disorders, CP messaging
● Activated Natural Community Supports:
Engagement, mobilisation and support to community organisations (communication for development activities) on SCD and MNS awareness—raising campaigns,</td></tr>
</table>

		support to community leaders in promoting child and family wellbeing ● **Strengthened Care Systems:** Training of professional and lay staff in coordinated PSS and NPA care for patients with SCDs and MNS and families; development of functional referral systems for at-risk patients and families

Barriers	**Strategic Actions are to be facilitated by:**
Lack of coordinated PSS and NPA systems. Stigma/discrimination of children/caregivers with SCD and MNS disorders/disabilities. Lack of financial/human resources. Lack of technical expertise; and Lack of shared community	**Community mobilisation**: Identifying, activating and strengthening local capacity; meaningful and inclusive engagement of patients and family wellbeing stakeholders. **PSS and NPA system strengthening:** Strengthening supports within existing structures, including functional referral systems and capacity among professional and lay providers in quality MHPSS care. **Integrating PSS and NPA across sectors**: Mainstreaming PSS and NPA across the health system – *social protection, health and nutrition, education, WASH and shelter systems*.

Classification and Benefits of Psycho-Social Support and Non-Pharmacological Approaches for Pain Management especially in addressing opioid dependence and abuse among the SCD patients

Over 50% of chronic opioid use begins in the acute care setting, after surgery, or for treatment of acute injury related pain (Callinan, Neuman, Lacy, Gabison, & Ashburn, 2017). Nonpharmacologic therapies have demonstrated benefit for acute pain with opioid sparing in hospital settings for inpatient post-operative pain and for acute pain not related to surgery.

The psychosocial support (PSS) and Non-Pharmacological approaches (NPA) for the care of people (and their families) with SCD are hereby classified as management and prevention therapies with distinct goals and intended outcome as outlined below.

1. **Intervention Classification of PSS and NPA for Pain the Management in SCD and Benefits**

1.1. **SCD Peer-support Group Therapies:** These social (e.g., dyadic and group therapies aim to improve adaptation to illness through contact and support with peers

Benefit: Peer Support therapy is clinically effective in improving pain in both children and adults and for enhancing reduction of the degree of pain sensation and pain interference

1.2. **Educational/Psychoeducational Therapies**: These aim to enhance adaptation to illness through information regarding the disease process and management

1.3. **Skill-based Training Therapies**: These include or require explicit practical training, or the presence of a trained practitioner, to enhance illness adaptation. Examples are cognitive behavioural therapy, biofeedback, hypnosis, massage, acceptance and commitment therapy, aquatic rehabilitation.

Benefits

a) CBT: This is CBT is an effective non-pharmacological intervention for persons with SCD. It is based on psychological principles and may involve the presence of a parent or family member.

Benefits of CBT include significant reductions in pain, improvements in pain, reductions of pain, significant decreases in pain, mild improvements in physical health

b) Dyadic Therapy: Dyadic Treatment is a form of therapy in which the infant or young child and parent are treated together. A clinician is present with the parent-child dyad, Dyadic therapies involve treatment delivered to a parent and child simultaneously. Several manualized dyadic approaches have shown evidence of effectiveness in treating social-emotional and behavioural problems in young children.

c) **Physical Contact Therapies/Modalities:** Physical modalities refer to any therapeutic medium that uses the transmission of energy to or through the patient. Physical modalities, such as thermotherapy (heat or cold therapy), electric therapy, and low-power laser therapy, are commonly used in rehabilitation practice to relieve pain and increase the flexibility of joints and soft tissues in patients with rheumatic disorders.

Physical forces such as heat, cold, pressure, water, light, sound, or electricity can be used as adjunctive treatment for the purpose of decreasing pain. In general, physical modalities are not meant to replace medical or other interventions; rather, they are intended to enhance overall outcomes. Massage therapy is indicated for SCD to provide pain relief, reduction of swelling or mobilisation of adhesive tissues.

Benefits of Physical Modalities:

i. **Massage therapy:** Benefits include

- statistically significant reductions in sensory pain scores,
- reduction in opioid use and number of hospitalizations.
- Induce local biochemical changes that modulate local blood flow and regulate oxygenation in muscles,
- influence neural activity at the spinal cord segmental level, thereby modulating the activities of subcortical nuclei that influence both mood and pain perception.

- increase the pain threshold at the CNS level by stimulating the release of neurotransmitters such as endorphins and serotonin.
- inhibit T-cells in the spinal cord that project into the CNS, leading to pain relief,
- increase local blood circulation,
- improve muscle flexibility,
- intensify movement of lymph, and loosened adherent connective tissue.

ii. Benefits of **Acupuncture** (random use of acupuncture needles anywhere on the body) include decreased pain scores immediately following acupuncture

iii. Benefits of **Aquatic rehabilitation program** include statistically significant reduction in pain along with increased respiratory muscle strength

iv. **Electrical stimulation (E-Stim)**: Electrostimulation is a strategy for modulating the nervous system by electrical stimulation. It is gaining popularity within the field of neurological physiotherapy. The different modes of electrical stimulation are muscle stimulation via the motor nerves, which is intended to produce a muscle contraction, and transcutaneous electrical nerve stimulation (TENS), which uses lower intensity stimulation and does not produce contractions. It takes advantage of the mechanism of neural signalling the electrical and chemical means by which action potentials are propagated, neurotransmitters are released, and neurons or target organs (e.g., muscle) are activated.

Benefits of E-Stim:

- E-Stim is an effective nonpharmacologic therapies for the treatment of numerous acute and chronic pain conditions.
- Patients can safely use E-Stim modalities such as hot and ice packs and transcutaneous electrical nerve stimulation (TENS) at home,
- E-Stim modalities are more useful for chronic pain management such as the treatment of wounds of various etiologies.
- E-Stim modalities may decrease pain from ischemia, augment blood flow in lower extremities with an impaired calf or foot pump and stimulate angiogenesis.
- Electrical stimulation is sometimes used to induce hypertrophy and improve blood flow.

v. **Exercise Therapy**: Aerobic exercise, 20 minutes daily.

vi. **Chiropractic Therapy**: Chiropractic therapy in the form of spinal manipulation and mobilisation may also be used in the early management of occipital neuralgia and is used specifically when a symptomatic spinal segmental joint dysfunction is believed to be the origin of symptoms

Chiropractic manipulation may not be safe in children.

vii. **Osteopathic Manipulative Treatment (OMT)**: The goal of OMT is to treat somatic dysfunction. OMT is based on four principles:

- the person is a unit composed of body, mind, and spirit;

- the body is capable of homeostasis, self-healing, and health maintenance;
- structure and function are interrelated; and
- rational treatment is based on an understanding of the above principles

Treatments are either "direct," in which the physician engages a patient's restricted plane of motion, or "indirect," in which the body is placed into a position of ease during treatment. OMT requiring a therapeutic correcting force is called an "active" treatment when provided by the physician and "passive" when provided by the patient.

d) **Alternative Foundations:** Examples are prayer, acupuncture, acceptance-based therapy

i. Benefits of healing touch therapy include decreases in physiological measurements of pain

e) Other Integrative Therapies

i. Biofeedback: Benefits include statistically significant improvements in pain intensity, pain episodes, and amount of pain medication needed

ii. **Hypnosis**: Benefits include reduce the number of pain days and amount of pain-related medication consumed when combined with CBT , non-significant improvements in pain, medication usage, and pain-related hospitalisation

iii. **Guided imagery**: statistically significant reductions in pain episodes and pain intensity

iv. **Creative Art, Music and Dance Therapy**: Art, dance, and music therapy are a significant part of complementary medicine in the twenty-first century. These creative arts therapies contribute to all areas of health care and are present in treatments for most psychologic and physiologic illnesses. Thinking about and creating art can help to distract you from pain and anxiety. Many art therapists believe this type of therapy works, in part, because creating art influences brain wave patterns and the substances released by the brain. It helps people express hidden emotions. It reduces stress, fear, and anxiety.

v. **Mindfulness-based Interventions**: These include such as Mindfulness-based Stress Reduction (MBSR) and Acceptance and Commitment Therapy (ACT).

ACT is a cognitive-behavioural approach with some similarity to exposure-based therapy, created as a descendent of radical behaviourism, with the central part of the approach initially suggested by Marlatt (1985). The fundamental goal of ACT is to increase psychological flexibility, or the ability to contact one's unwanted internal experiences in the service of engaging in values-consistent behaviour. Psychological flexibility is cultivated through six interrelated core processes, including acceptance, cognitive defusion, contact with the present moment, self-as-context, values, and committed action. ACT utilises metaphors (e.g., floating leaves on a moving stream) and experiential exercises to promote experiential acceptance (e.g., encountering one's thoughts and feelings without judgement or aiming to control them) and a commitment to one's actions to move toward a more valued life.

1.4. **SCD Pain target:**

1.4.1. **Acute Pain:** PSS and NPA for pain such as acute pain, acute recurrent painful crises, neuropathic pain, or chronic pain include Massage, yoga, virtual reality, and guided audio-visual relaxation in addition to medications (e.g., opioids, NSAIDs).

1.4.2. **Chronic Pain:**

Chronic pain is pain that lasts or recurs for more than three months. Chronic pain is complex in terms of aetiology and management approaches, and despite the existence of pharmacological therapy remains highly resistant to treatment (Oluwatoyin Olatundun Ilesanmi, 2010). Chronic pain significantly and negatively impacts upon individual lives, leading to physical disability, mental health problems and long waitlists for specialist health services, as well as economic costs to health services, patients and the community

PSS and NPA for chronic pain of unclear aetiology, chronic pain related to an objective cause, chronic neuropathic pain, or "breakthrough" pain are (Oluwatoyin Olatundun Ilesanmi, 2013):

a) Cognitive Behavioural Therapy and other integrative approaches (e.g., acupuncture, massage therapy) in addition to medications as part of a comprehensive disease and pain management plan.

b) Cognitive-behavioural interventions focus on the identification and modification of thoughts, feelings, and behaviours using various techniques such as relaxation, distraction, biofeedback, and cognitive restructuring. These techniques aim to reduce the subjective experience of, or increase the tolerance to pain

Note:

- Specificity related to the type of pain targeted by the intervention may help improve clinical decision making and the pairing of the correct intervention to pain type, just as one would do for a pharmacological intervention (e.g., right patient, right drug, right dose, right time, right route).

1.5. Duration of PSS and NPA Intervention Sessions for pain reduction

These are either single-session interventions or multi-session interventions for reducing acute or chronic pain

1.5.1. Single-Session Interventions: Interventions that can be delivered in a single-dose format may be especially useful for persons with SCD because of transportation difficulties (getting to and from clinical appointments), frequent hospitalizations, and physical disabilities, all of which can make it difficult to have reoccurring (weekly, bi-weekly) appointments that require physical presence. **S**ingle-session interventions may be conducted for acupuncture and hypnosis to reduce pain.

1.5.2. Multi-Session: Multi-session interventions for pain reduction in various delivery modes, such as face-to-face, teleconferencing, and/or internet-based sessions

2. Prevention of SCDs:

Primary prevention aims at preventing SCDs

2.1. Primary Prevention: Primary level prevention of SCD is emphasised. Management at Primary Health Care level includes prevention of disease complications, e.g. provision of psycho-social support to affected individuals and their families.

2.1.1. Psychosocial Strategies for primary prevention of SCDs

The PSS strategies include:-

a) Public awareness creation, community sensitisation and advocacies on SCDs and its associated complications

b) improved access to, and quality of PSS and NPA

c) Preconception methods of prevention: At-risk couples need to be identified and offered PSS, genetic counselling and information on prevention

d) **Grief Counselling:**

e) **Genetic Counselling**: Genetic Counselling includes the provision of information necessary for rational decision-making regarding prenatal testing, termination of pregnancy and the prevention of SCDs, as well as referring the family for appropriate services and care.

This process involves the following: -

i. comprehension of medical facts, diagnosis, prognosis and management of SCD.

ii. appreciation of SCD and risk of recurrence in off-springs.

iii. understanding the options for dealing with the risk of recurrence.

iv. choice of an appropriate course of action in view of the risks and family goals; and

v. making the best possible adjustment to the disorder within the family.

2.2. **Secondary Prevention**: Secondary prevention aims at the pre-natal identification of women at increased risk for having a child with SCDs. Secondary level prevention includes voluntary pre-natal diagnosis and PSS for selective termination of pregnancy for SCD, other genetic disorders and birth defects

2.2.1.Psychosocial Strategies for primary prevention of SCDs:

The PSS Strategies for secondary prevention of SCDs include:

a) identification of pregnant women at risk;

b) Refer affected individuals for early stimulation programmes

c) Provide appropriate PSS for anticipatory guidance and genetic counselling

3. Tertiary prevention: These are specialist care that is rendered at central hospitals.

3.1. **Psychosocial Strategies for tertiary prevention of SCDs**

Strategies for the psycho-social support of affected individuals and their families include:-

a) anticipatory guidance for the prevention of SCD related crises

b) PSS for coping with SCD related complications

c) rehabilitation of disabilities associated with SCDs

Roles of the PSS and NPA Providers

In view of the existing complex relationship between medication use and the pain experienced by SCD patients, especially regarding opioid analgesia,

1. PSS and NPA interventions should be age-appropriate, and available in both hospital- and community-based settings

2. Clinical psychologists working with the sickle cell team should formalise assessments and therapies with children at the age of about 7 years, which is developmentally suitable for both individual and group/family work. However, if the team does not include a psychologist, haematologists should seek the help of other health professionals such as specialist nurses, to assess patients initially and then refer them to a psychology service as appropriate.

3. **Communication**:

a. Patient report of pain is the gold standard.

   i. There are no vital sign changes or lab values that confirm or rule-out a sickle cell pain crisis

   ii. Do not refer to patients with SCD as "sicklers," as this is a derogatory term

   iii. Requests for specific pain medicines/doses are most commonly due to past experience, not drug-seeking behaviour for opioid use

b. Build trust by believing the patient is in pain:

   i. Patients may not be glad to see you – show them you are here to help

   ii. Negative emergency hospitalisation experiences in the past may make them guarded or mistrustful

   iii. Pain can make anyone irritable, impatient, or upset

   iv. Empathetic nonverbal communication is essential (eye contact, facial expression, gestures)

   v. Be patient when asking questions; it is often difficult to speak when in severe pain

   vi. Patients may bring a caregiver with them, as it may be difficult to understand treatment plans and ask questions when in severe pain.

Goal and Objectives of PSS and NPA

Goals:

PSS and NPA programmes ultimately aim to (1) reduce and prevent harm, (2) improve mental health and psychosocial wellbeing, (3) strengthen resilience to recover from SCD painful crises, and (4) improve the care conditions that enable patients and families to survive and thrive.

The overall goal of the policy guidelines is to help patients cope better, fulfil roles and to achieve a better quality of life. It offers practical information and tools to implement a range of PSS and NPA interventions to rapidly address the protection and psychosocial support needs of patients with SCDs and their families, in parallel with tailored medical interventions in home and clinical settings.

Specifically, this policy guidelines aims to:

- offer psycho-social support and Non-Pharmacological Approach to Pain Management as standard care in the management of SCD, adjunctive to routine medical treatment.
- reduce the burden of SCD as a genetic disorders and birth defects to the individual, the family and society in general
- empower individuals with SCD, other genetic disorders and birth defects, and their families, to live and reproduce as normally and responsibly as possible, and
- create awareness of the psychosocial and fiscal impact of SCD, other genetic disorders and birth defects

- provide opportunity for the long-term care of SCD patients and their families – including specialised psychological and social services for those with mental, neurologic and substance abuse (MNS) disorders, protection risks or other serious distress.

Objectives:

Main Objective

The main objective is to offer an operational framework that emphasises engaging actors at all levels (children, caregivers, families and community service providers) to design and implement PSS and NPA strategies that are locally relevant, comprehensive and sustainable for pain management in order to effectively restore, strengthen, and mobilise family and community supports and systems with the ultimate goal of supporting SCD patients and family well-being in in Nigeria.

Specific Objectives

a) To provide a national, PHC-based, comprehensive, PSS and NPA for the diagnosis and care (management and prevention) of SCD, genetic disorders and birth defects in Nigeria.

b) To integrate PSS and NPA into primary, secondary and tertiary levels of care as part of the comprehensive health care system with an appropriate referral network.

c) To develop a PSS and NPA component of health services through capacity building, re-orientation of health professionals, training of PHC workers particularly midwives, nurses and others concerned with Maternal, Child and Women's Health.

d) To establish the infrastructure and technology with which to deliver PSS and NPA services effectively and equitably to the community at large.

e) To develop appropriate public education and community awareness for health promotion strategies via PSS and NPA for SCD management in Nigeria

f) To provide a framework to support and promote safe, nurturing environments for persons with SCDs, psychosocial wellbeing and protection

g) To restore, strengthen and mobilise family and community supports and systems that ultimately support patients and their family wellbeing by improving the care conditions that enable them to survive and thrive.

h) To increase public awareness regarding PSS and NPA

i) To reduce stigma and discrimination associated SCDs.

j) To promote and protect the human rights of people living with SCDs

k) To ensure that the planning and provision of PSS and NPA is evidence-based

Categorization of Care using PSS and NPA for SCD Management

Levels of Care

1. **Home / Family Level:** It involves the health of the whole family members. Within the family micro-environment, patients with SCD need optimal family support, understanding and care, particularly in terms of providing adequate nutrition, and health care delivery to achieve an optimum and steady state of health

   Strategic PSS and NPA Interventions:

   - Public Awareness Creation and health promotion via the various media, health care workers undertaking home visits, or outreach programmes.

- Engagement with the SCD patients, spouse/partner, the parents, other family members and caregivers, teachers and other community

2. Community-based PSS and NPA:

Several interventions can be labelled as community-based PSS provided they are part of a more strategic psychosocial and mental health approach with the aim to build on existing individual and community resources, capacities and resilience for pain management.

Strategic Community-based PSS and NPA Interventions:

a) **Strengthens natural supports and systems**: This approach works with and through a community's natural supports and systems to contribute to a stronger overall care environment, which promotes inclusion of SCD patients and their families in existing supports and reduces the potential for stigma. Mapping and systematically building on local resources such as community networks, practices and processes helps to build scalable and sustainable programmes.

b) **Capitalise on Usage of Community Knowledge and Capacities**: The community-based psychosocial support and non-pharmacologic approaches to pain management recognize that all people, including SCD patients and their caregivers, have skills, assets, and resources for coping. Their coping capacities vary based on individual and environmental characteristics and may be undermined or weakened by the chronicity of SCD crises. It is, however, clear that families and communities know the risks and resources in their environment, and the factors that support and hinder the wellbeing and protection of SCD patients and families.

Strengthening resources and capacities for self-help makes best use of people's knowledge and capacities to recover, and to help the SCD patients do the same. PSS and NPA Interventions that engage participation by the community are more likely to be meaningful and sustainable – and to help restore patients' sense of competence and self-agency to meet new challenges and be hopeful about the future.

c) Build the competencies, capacities and skills of local practitioners and provide resources to carry out PSS and NPA programmes in line with the principle of 'do no harm'.

d) **Community Engagement:** A community-based approach entails a process of community engagement and involvement through all phases of the programme cycle – assessment, design and implementation and M&E. Community involvement ranges from partnership to ownership, depending upon the situation and the community's resources to implement and sustain interventions. Given the mandate to 'do no harm', it is essential that interventions do not damage natural community support. Instead, they must identify, engage and work within existing supports

e) The IASC MHPSS Pyramid of care: Address issues in the MPHSS pyramid of care for SCD patients.

Strategic PSS and NPA Interventions:

The four layers in the system of supports for patients' recovery and wellbeing are:

- **Social Considerations**: It represents the foundations of wellbeing for all people affected by the SCD crisis. It ensures that basic PSS and NPA services and security are delivered in a way that is participatory, safe and socially appropriate to ensure the dignity and wellbeing of all patients and community members

- **Family and Community Supports**: Family and community supports for recovery, strengthening resilience and maintenance of mental health and psychosocial wellbeing of children and families.

- **Focused Care**: Trained and supervised workers offer focused, non-specialized support, including general (non-specialized) social and primary health services to SCD patients and families.

- **Specialised Care**: Specialised services by mental health clinicians and social service professionals for SCD patients and families beyond the scope of general (non-specialized) social and primary health services.

f) Engagement of lay and professional services for psychological and social supports

Strategic PSS and NPA Interventions:

Lay Actors: Lay people who receive proper training and regular supervision by mental health clinicians can provide scalable PSS interventions to support SCD patients suffering from depression, anxiety, and stress. Lay and professional actors work together across the pyramid to meet the community's needs. Both lay and professional support providers require certain competencies to do their tasks. Establishing minimum qualifications and standards of lay and professional PSS and NPA providers is an important aspect of a community-based approach.

With training and supervision, lay people can provide nonclinical psychosocial support to children and families, such as:

- Peer support.
- Cultural and recreational activities for SCD patients.
- Identification of vulnerable families for referral to specialised support.
- Psychological first aid (PFA), which includes assessing needs and concerns; helping patients address basic needs; listening to and comforting patients and helping them feel calm; helping connect to information, services and social support; and protecting them from further harm (Organisation, 2011)

3. **Clinical Practice Settings:** At the clinical practice settings, clinicians should consider effective psychosocial support and nonpharmacologic approaches for pain management

Strategic PSS and NPA Interventions:

a) Priority PSS and NPA Services Prior to Conception

i. **Target population**: Women of reproductive age and individuals and families at high risk for SCD, genetic disorders and birth defects

ii. **Psychosocial Support**

- Creation of awareness of risks associated with advanced maternal age
- Ascertainment of genetic risk for SCD
- Discouragement of sexual relationship with two HbAS and between HbAS and HbSS persons
- Creation of awareness of Genotypes that predispose to SCD

b) Services During Pregnancy

PSS services during pregnancy should include genetic counselling, prenatal diagnosis and the option of termination of pregnancy.

i. **Target population:**

- Women of reproductive age and individuals and families at high risk for SCD genetic disorders and birth defects

ii. Psychosocial Support

- During regular ante-natal care

- Early identification of pregnant women of advanced maternal age
- Ascertainment of genetic risk based on spousal genotype status
- Offering of appropriate diagnostic tests

c) Services at Birth

i. **Target population**: Parents and their newborns, and individuals who have undergone selective termination of pregnancy

ii. **Psychosocial Support**

- Screening of the neonate for SCD (Newborn Screening)
- Physical examination of the neonate for SCD
- Parental referral for PSS and genetic counselling

d) PSS Services in Infancy and Childhood

Many genetic disorders and birth defects are not recognisable at birth.

i. **Target population**: Children and their families

ii. **Psychosocial Support**

- Encouragement of attendance at PSS well-baby clinics
- Monitoring of growth and development
- Referral for appropriate care and genetic counselling

e) PSS Services for Adolescence and Adulthood

i. **Target population**: All adolescents and adults with SCD experiencing:

- suffering acute, chronic and severe pain
- Avascular necrosis
- Priapism
- Acute chest syndrome
- Stroke
- Splenic complications
- Infection and sepsis
- Organ failure
- Psychosocial complications

ii. **Psychosocial Support**

- Referral for appropriate care and genetic counselling

Any investigation/Test/Screening required

Good pain management consists of establishing the diagnosis using appropriate investigations, and providing the individual or family with genetic counselling, psychosocial support, and the best possible medical treatment.

The following are some of the investigation/Test/Screening required for PSS and NPA interventions in pain management:

1. **Acute Pain**: Conduct a comprehensive pain assessment.
2. **Chronic Pain**:
    a. Perform a comprehensive patient assessment and history.
    b. Obtain a thorough medication history.
3. **Avascular necrosis:** Conduct a thorough chronic pain assessment (type of pain and underlying mechanism) and maintain a high index of suspicion for AVN.
4. **Priapism:** Investigate the potential psychological effects (e.g. anxiety) the condition may have on patients.
5. **Stroke:**
    a. Conduct neurologic assessments routinely in children and adults and maintain a high index of suspicion for SCI in patients who demonstrate neurologic deficits.
    b. Assess parents' understanding of the need to seek care for any emerging neurologic symptoms.
    c. Assessment of poor academic performance as a signal of neurocognitive deficits resulting from SCIs
6. **Splenic complications**: Conduct a thorough assessment of abdominal pain, closely monitor temperature, and anticipate the need for a sepsis evaluation.
7. **Psychosocial complications**: Assess patients, especially those with frequent emergency departments (ED) visits and hospitalizations, for the presence of psychosocial health complications, to identify any who may benefit from social work, psychiatric, or case management referral.
8. **Neuropsychological Assessments**:
    a) Neuropsychological screening for patients with SCD provides a useful means of identifying those who require support, particularly adequate educational provision
    b) **Normal or Abnormal Magnetic Resonance Imaging (MRI)**: This can be used to determine learning deficits in reading and mathematics, and other intellectual functioning associated with silent infarcts (silent strokes) in children with SCD.
    c) Measures of attention/concentration and executive functioning tend to be valuable as predictors of neurological pathology and should be included in the initial assessments. These assessments should be initiated at 5 years of age, when a child starts school.
    d) Neuropsychological rehabilitation should be considered following any assessments, and patients should be referred to a Neuropsychology Service where indicated.

e) Additional or special educational support should also be considered, this could compensate for the effects of strokes and silent infarcts.

f) Liaison with education departments, educational psychologists and schools is very important.

9. **Culturally informed stress-coping-adjustment framework**: This can be used to assess and address the psychological status, psychosocial functioning, and disease outcomes of individuals with SCD

10. **Psychological Adjustment to SCD**:

This is usually a result of the relationship between illness parameters (SCD severity – phenotype, complications and pain frequency), demographic parameters (age, gender and socio-economic status), and hypothesised adaptation processes (stress appraisal, coping methods and family support) that mediate the illness/demographic factors and outcome.

a) Good and Poor Adaptation to SCD

i. Good psychological adjustment in children and adults may be indicated by various factors, including lower levels of perceived daily stress, reduced negative or passive coping strategies and appropriate family functioning (increased family support and lessened family conflict).

ii. **The Transactional Model of Stress and Coping**: This was developed by Lazarus & Folkman (1984). It views SCD as a potential stressor to which the individual and family attempt to adapt. The model can be used to outline the processes associated with the patient's and family's good and poor adaptation to SCD

Note

1. **Psychological Coping**: The following pain coping questionnaire and inventory can be adapted to determine how patients live with and psychologically overcome SCD:

a) **McGill Pain Questionnaire**

b) **Coping strategies questionnaire (CSQ)**: This was developed by Rosentiel and Keefe (1983)

c) **Coping inventory for SCD (CSQ-SCD)**: This was developed by Gil et al (1989). It has 13 subscales which have been grouped into:

i. **Active Coping/Coping Attempts (e.g.** distraction and increased activity)

ii. **Affective Coping / Negative Thinking** (negative thoughts and feelings, coupled with 'passive' psychological but useful coping methods). This can be used to determine frequency of pain episodes, pain severity, health service utilisation (emergency visits) and hospitalizations.

iii. **Passive Adherence Coping**: For example, rest and taking fluids.

Components and Designs of PSS and NPA in Pain Management for SCD Patients and Families

1. Individual Therapy

a. **Sickle Cell Disease Educational Programs**: The disease education should consist of psychoeducational programs and cathartic activities (eg, writing or drawing about SCD), disease information, Child and adolescent health issues related to SCD, Reproductive health issues related to SCD, and effective communication with the health care team.

b. **Cognitive-behavioural Therapy (CBT)**: The cognitive-behavioural therapy intervention may consist of 4 weekly classes aimed at delivering individual training in distraction, relaxation, and imagery skills, as well as videotapes, audiotapes, and written materials for practice.

c. Biofeed-back and relaxation training:

d. **Self-hypnosis**: This selfcare intervention may improve coping with pain in children and adolescents with SCD

e. **Art Therapy**: This is a specialised training intervention that focuses on innovative strategies for SCD patients to express their feelings about pain through art and helping them share their experiences.

f. **Attention-control Therapy**: The attention-control condition involves SCD patients spending the same amount of time (4 weekly sessions) engaged in fun activities (eg, picnics, museums).

g. **Behavioural Contracting**:

h. **Coping Skills Training in 3 key skills**: Deep breathing/ counting relaxation, pleasant imagery, and Calming self-statements. These techniques can be audio-recorded instructions and given to patients as homework assignments to encourage daily practice. Patients can receive a phone reminder to practice the skills and attend a brief review session approximately 1 week after the initial training session.

i. Individual psychoeducation and skills training in deep breathing/relaxation, imagery, and calming self-statements

Expected Outcomes:

These pain management interventions for SCD may result in:

- Improved overall assessments,
- decrease in percentage of days with pain
- compliance with routine health service use,
- Increase SCD knowledge, and
- Improved family cohesion

2. Group Therapy:

a. **Cognitive-behavioural Techniques**:

- CBT may also be delivered in a group setting n for adolescents and adults with SCD. It may be conducted as a weekly 1-hour group session for 2 months, resulting in 8 total hours of therapy.
- In the group setting, participants will learn to identify and modify maladaptive pain-related cognitions, change the meaning they assign to their pain, and increase perceived control over pain.
- The participants should also receive relaxation training (eg, progressive muscle relaxation) and health education, and completed weekly homework assignments for skill practice

b. Culturally and developmentally sensitive psycho-educational group intervention

c. Sickle Cell Disease Educational Programs:

d. Self-help and support groups:

e. Group therapy focused on modifying maladaptive pain-related cognitions, increasing perceived control over pain, relaxation training, and health education

f. Attention-control group Therapy

Expected Outcome

These pain management interventions for SCD may result in:

- greater usage of positive coping strategies and engagement in behavioural activities, higher self-efficacy and perceived self-control for pain management.
- Reduction of the affective component of pain in SCD crises

3. **Family-based Counselling and Therapy:**

a. It focuses on families as interactive systems, with the goal of formulating change at the family (rather than individual) level.

b. **Cognitive-behavioural Techniques**:

- The family-based interventions incorporate cognitive-behavioural coping skills intervention to improve pain coping strategies and decrease pain perception
- RCT of a family-based cognitive-behavioural intervention may reduce pain and improve health-related and psychosocial outcomes among adolescents with SCD

c. Brief pain intervention:

d. **SCD Education**: The disease education should consist of psychoeducational programs and cathartic activities (eg, writing or drawing about SCD), disease information, Child and adolescent health issues related to SCD, Reproductive health issues related to SCD, and effective communication with the health care team.

e. Family-based therapy including training in deep breathing, relaxation, positive coping statements, and guided imagery

f. Sickle Cell Disease Educational Programs

Expected Outcomes:

These pain management interventions for SCD may result in:

- Change in pain, health service utilisation, pain-related hindrance of goals, pain coping, and psychosocial outcomes (eg, disease knowledge, self-efficacy, family communication)

4. **Non-Opioids:** These are nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. These medications tend to be used on their own for mild to moderate pain or in conjunction with other medications for more severe pain. Both of these agents ameliorate pain by reducing inflammation.

Steps in PSS services for patients living with SCD if any and how to strengthen such services.

Basic steps for incorporating Psycho-social support and Non-Pharmacological Approach to Pain Management in Practice Settings include:

a) Identify the most important components of Psycho-social support and Non-Pharmacological Approach relevant to the sickle cell population.

b) Develop strategies for matching Psycho-social support and Non-Pharmacological Approach to individual requirements and readiness for behaviour change.

c) Testing the efficacy of different therapy formats – eg. individual versus group.

d) Broaden the scope of Psycho-social support and Non-Pharmacological Approach to address issues other than pain – eg. quality of life, occupation, and access to health services.

e) Address culturally sensitive needs.

f) Develop an appropriate Psycho-social support and Non-Pharmacological Approach for managing sickle cell disease and pain.

g) Develop Self-Help Manual for Psycho-social support and Non-Pharmacological Approach/programme that will assist individuals in both learning and maintaining appropriate psychological coping strategies

h) Ensure clients' participation in the development process

Definitions of Terminologies

Child: Child is defined as all children and adolescents aged 0-18 years of age (according to the Convention on the Rights of the Child).

Caregiver: Caregiver refers to those responsible for the care of children with SCDs, and may include mothers and fathers, grandparents, siblings, and others within the extended family network, as well as other child caregivers outside of the family network.

Cognitive Behavioural Therapy (CBT): Cognitive behavioural therapy (CBT) comprises two psychological approaches, that is, cognitive and behavioural techniques. The premise underlying CBT is that difficulties in living, relationships, general health, etc., have their origin in (and are maintained by) thoughts, emotions and behaviours. The aim of cognitive interventions is to challenge and ultimately change, inappropriate self-defeating thoughts to enable the patient to lead a more productive and satisfying life. On the contrary, behavioural methods arise from the premise that inappropriate behaviours are learnt, and therefore can be unlearnt. CBT seems appropriate for treating patients with SCD, as the illness and pain cause much distress and suffering to them. CBT can be offered to patients with SCD individually or in groups. There is some evidence to suggest that CBT helps to reduce health service utilisation in both children and adolescents with SCD (Broome, Maikler, Kelber, Bailey, & Lea, 2001). CBT in adults with SCD reduces pain (Thomas, 2000), and improves mood and psychological coping ability

Community: Community includes men and women, boys and girls, and other stakeholders in child and family wellbeing, such as teachers, health workers, legal representatives and religious and governmental leaders. Community can be defined as a network of people who share similar interests, values, goals, culture, religion or history – as well as feelings of connection and caring among its members.

Community Mobilisation: Community mobilisation is efforts made from both inside and outside the community to involve its members (groups of people, families, relatives, peers, neighbours or others who have a common interest) in all the discussions, decisions and actions that affect them and their future with regards to the psychosocial management and prevention of SCD

Community Participation: Community participation is the process by which individuals, families or communities assume responsibility for their own welfare and develop the capacity to contribute to their development. Community participation refers to an active process whereby the beneficiaries influence the direction and execution of projects rather than merely receive a share of the benefits.

Culture: Culture is a set of shared values, beliefs, and norms among a society. Culture is dynamic, changing as societies adapt to new information, challenges, and circumstances.

Family and Kinship: Family is a socially constructed concept that may include children who live with one or both biological parents or cared for in various other arrangements such as living with grandparents or extended family members, with siblings in child- or youth-headed households, or in foster care or institutional care arrangements. Kinship indicates culturally recognized relationships defining roles and obligations between individuals and groups. In many contexts, kinship relationships extend far beyond those included in the conventional idea of a "nuclear family".

Genetic Counselling: This is a communication process which aims to assist individuals or families with a genetic disorder or birth defect to understand the medical implications, diagnosis, prognosis, and management of the disorder; the inheritance pattern and risk of recurrence; the options available to deal with the risk and the choices and actions required; and how to make the best possible daily life adjustment to the disorder.

Genetic Disorder: This is a pathological condition due to a mutation in one or more genes. Such a gene has mutated (changed) so as to increase the risk of or cause a genetic disorder.

Genetic Services: These are services forming part of integrated comprehensive health care, aimed to assist individuals with a genetic disadvantage to live and reproduce as normally and responsibly as possible. The components include clinical diagnostic services, counselling, laboratory support, prevention strategies, public awareness campaigns in collaborations with NPOs, and training. All medical genetic services should be comprehensive.

Neuropsychology: The risk of neurocognitive impairment is particularly important in children and adolescents because of educational implications. Consequently, there is a need for comprehensive neuropsychological assessments

Psychoeducation: Psycho-educational interventions should primarily focus on improving the knowledge and understanding of patients regarding their illness, while at the same time providing psychological support. The assumptions underlying this approach emphasise that firstly the information can lead to improved knowledge and better coping with the condition. Secondly, patients who feel isolated may benefit from the support and motivation of others through shared experience. Psychoeducation can be offered to children and adolescents with SCD in peer or family groups. It has been demonstrated that group interventions help to identify issues and concerns in children and adolescents with SCD (Anie, 2005), while family interventions improve knowledge in children and adolescents with SCD (Kaslow et al., 2000).

Psychosocial and Genetic counsellors: These are, appropriately trained psychosocial and genetic counsellors who provide information and psychosocial support to individuals or families who have, or who are at risk for SCDs, other genetic disorders or birth

defects. These counsellors identify such individuals and families, investigate the clinical problems, interpret medical information to the clients, analyse inheritance patterns and risks of recurrence, review available options with the clients, and educate the community about genetic disorders.

Resilience: Resilience is the ability to overcome adversity and positively adapt after challenging or difficult experiences. Children's resilience relates not only to their innate strengths and coping capacities, but also to the pattern of risk and protective factors in their social and cultural environments.

Well-being: Well-being describes the positive state of being when a person thrives. In mental health and psychosocial work, wellbeing is commonly understood in terms of three domains:

a) **Personal wellbeing** – positive thoughts and emotions such as hopefulness, calm, self-esteem, and self-confidence

b) **Interpersonal wellbeing** – nurturing relationships, a sense of belonging, the ability to be close to others

c) **Skills and knowledge** – capacities to learn, make positive decisions, effectively respond to life challenges, and express oneself

CHAPTER 12

SICKLE CELL DISEASE CARE AT PRIMARY HEALTH CARE (PHC) LEVEL

12.1 Health Maintenance

Organizing Clinical Care- Encouraged all patients with SCD to enroll at the nearest SCD clinic and attend regularly on their clinic appointments dates

- Education and psychosocial support –
    - Nutrition, supplements (folic acid) and liberal oral fluid intake,
    - Have adequate Sleep
    - Allow to attend school and participate in sports support groups and social activities
    - Learn to share problems with love ones
    - Avoid extremes of cold or heat, physical exertion and anxiety

Travel management:

- Seek travel advice and accept all the offered immunisations relevant to the area to which they are travelling to; this includes live vaccines like yellow fever

- Carry adequate routine drugs
- Referral letter/ medical report/ID of SCD

General infection control measures:

- Teach and continually remind families of children or adults with SCD to seek immediate medical attention for fever (temperature greater than 38.3°C and other signs of infection
- Teach families of children with SCD and adults with SCD to own and learn how to use a thermometer. (Use axillary temperature in infants and young children.)

Immunization (Infection prevention):

- In addition to all the regular vaccines, make sure the child or adult with SCD receives vaccination for three bacteria that are very dangerous for people with SCD. They should be vaccinated against pneumococcus, Haemophilus influenzae type b (Hib), and meningococcus. They should also be on penicillin prophylaxis
- They should always be on malaria prophylaxis and use insecticide treated mosquito nets
- In addition to all the regular vaccines, make sure the child or adult with SCD receives vaccination for three bacteria that are very dangerous for people with SCD. They should be vaccinated against pneumococcus, Haemophilus influenzae type b (Hib), and meningococcus. They should also be on penicillin prophylaxis
- They should always be on malaria prophylaxis and use mosquito net

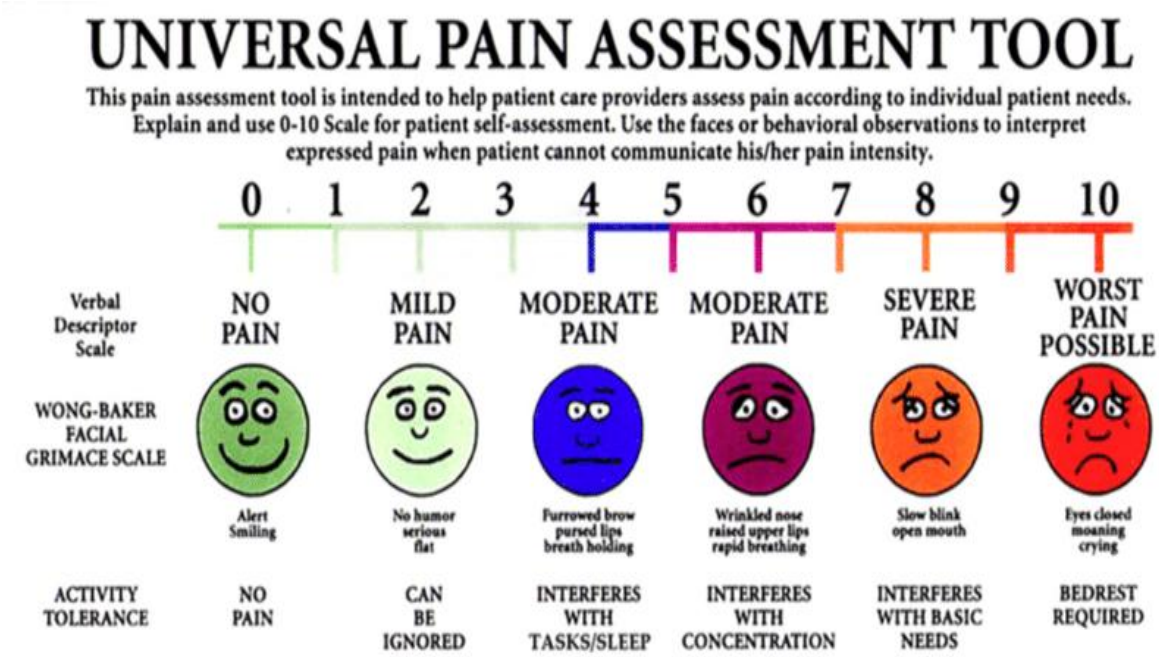
Reproductive Health:

- Encourage young male and female patients with SCD in reproductive age to seek medical advice on reproduction at the closest secondary or referral hospital where services for counseling on male reproductive health are available.
- Refer patient with SCD who wants to marry together with his/her intended partner to the closest referral hospital for pre-marital counseling with a view of the partner undergoing a haemoglobinopathy screening
- Educate on the use of contraception. No contraindications for any of the usual contraceptives
- Stop Hydroxyurea 3 months before conception.
- Prescribe routine prenatal vitamins.
- Encourage female patients to book and attend antenatal clinic for proper follow up during pregnancy.

12.2 Management of Acute Complications

Acute SCD pain (vasoocclusive pain episode, or "pain crisis")

- When pain crisis develops, decide quickly whether treatment is needed or not.
- Refer to a higher level of care when there is additional symptom such as, fever, breathing difficulty, severe headache, vomiting, or if the pain is different from the usual sickle cell pain
- If the pain is mild, comfort measures such as drinking fluids, local heat, massage, walking around, deep breathing exercises e.t.c. may be tried before using medication.
- Give IV fluids in moderate to severe pain especially if the patient is unable to drink well
- Administer analgesics based on pain score



Use 2-step method for use of pain medications for children:

- Step 1 - Mild pain - use acetaminophen (Paracetamol, Tylenol, etc) and anti-inflammatory medications such as ibuprofen (Brufen, Calprofen, Nurofen, etc)
- Step 2 - Moderate to severe pain: strong opioids such as morphine plus stronger anti-inflammatory medications such as naproxen, diclofenac, etc. OR refer to a higher level of care

Use 3-step method for use of pain medications for adults:

- Step 1- Mild pain - use acetaminophen and anti-inflammatory medications
- step 2 - Moderate pain: Use milder opioids eg dihydrocodeine OR refer to a higher level of care
- Step 3 - Severe pain: Strong opioids such as morphine plus stronger anti-inflammatory medications OR refer to a higher level of care

Acute Anaemia

- When there is sudden whitening of palms, lips or skin with difficulty in breathing, easy fatigue and weakness, quickly refer to higher level of care for further evaluation and treatment

Acute splenic sequestration –

- Educate parents and teach them how to feel for an enlarged spleen and liver and to go to the hospital early.
- Quickly refer to secondary or tertiary health care facility whenever patient with SCD has sudden, progressive abdominal swelling, easy fatigue, and increased awareness of heartbeats. Emphasize that it is a medical emergency
- Yellowness of the eye (jaundice) – Patient with rapidly deepening jaundice should be referred to a higher level of care for evaluation and treatment
- For all cases of anaemia requiring transfusion therapy, refer to secondary or tertiary hospital for treatment

Other Acute Complications of SCD

Stroke: Refer to a higher level of care if there is severe headache, dizziness or loss of consciousness.

Acute chest syndrome: Refer to a secondary or tertiary hospital if there is chest pain and breathing

difficulty with or without cough and fever .

Priapism – Painful, persistence unintentional penile erection

- Male SCD patients should be educated from childhood about priapism and encouraged to inform their parents/guardians or doctors if it occurs. Emphasize that it is a medical emergency.
- The following measures may help: going to the toilet to empty the bladder, use of pain killers, taking a warm bath or gentle walk. If it persists after two hours, refer to the closest secondary or tertiary hospital without further delay

12.3 Chronic Complications

Chronic Leg ulcers:

- Assess the wound thoroughly. Document the size, appearance, status of the surrounding skin, presence of tenderness, edema and femoral lymph nodes enlargement.
- Apply wet-to-dry dressings
- Give zinc supplementation
- Advise patient to elevate feet when sitting to improve blood circulation to the ulcer
- Treat the pain with adequate and appropriate analgesia.
- Explain to the patient that ulcer may take long time to heal. Also, enforce the prevention measures to reduce the risk of recurrence
- Refer to higher facility if there are features of osteomyelitis, arterial insufficiency or if malignancy is suspected

Avascular necrosis:

- Minimize movement and bearing of heavy weight on affected joint.
- Refer for further evaluation and intervention at a higher level of care.

Chronic Pain: pain lasting more than 3 months

- Refer to a higher health care facility for further evaluation and treatment

Ophthalmologic complications:

- Refer patients with ophthalmic conditions to an ophthalmologist

Psychological complications:

- Refer patients to the appropriate level of care for psychological assessment and interventions.

12.4 Hydration Guide

- Patients with SCD are at risk of dehydration due to impaired renal concentrating power and poor fluid intake
- Encourage oral fluids first, it should be used whenever possible
- Give IV fluids if the patient is unable to drink well, has severe pain, abdominal symptoms, or temperature is not settling
- Hydrate with normal maintenance fluid intake
- Use fluids recommended for IV therapy, usually 5% or D/S
- Stop IV fluids when the patient is stable or pain is controlled
- Maintain a strict input/output chart for every patient

- For children, weigh them daily

Summary

- There should be a network of care which include community, primary, secondary and tertiary care. Maintain clear communication between the different levels of care.
- Perform routine health checks and care for less severe complications.
- Educate parents and patients about the disease during each outpatient visit. Parents' understanding of the condition is vital. Offer strategies to manage mild symptoms at home. Educate them about the symptoms that require urgent medical assessment.
- Assess adherence to folic acid, penicillin prophylaxis and Hb level during visits
- Refer patients with major complications to specialized hospitals with appropriate facilities.

REFERENCES

1. National Population Commission (Nigeria) and ICF. National Population Commission (Nigeria) and ICF; Abuja and Rockville: 2019. Nigeria Demographic and Health Survey 2018.https://dhsprogram.com/pubs/pdf/FR359/FR359.pdf.

2. Nnodu OE, Sopekan A, Nnebe-Agumadu U. Implementing newborn screening for sickle cell disease as part of immunisation programmes in Nigeria: a feasibility study. Lancet Haematol. 2020;7:e534–e540. - PMC – PubMed

3. Nnodu OE, Oron AP, Sopekan A, Akaba GO, Piel FB, Chao DL. Child mortality from sickle cell disease in Nigeria: a model-estimated, population-level analysis of data from the 2018 Demographic and Health Survey. Lancet Haematol. 2021 Oct;8(10):e723-e731. doi: 10.1016/S2352-3026(21)00216-7. Epub 2021 Sep 2. PMID: 34481551; PMCID: PMC8460996.

4. Singer, D. B. Postsplenectomy sepsis. *Perspect. Pediatr. Pathol.* **1,** 285–311 (1973).

5. Luzzatto, L. Sickle cell anaemia and malaria. *Mediterr. J. Hematol. Infect. Dis.* **4,** e2012065 (2012).

6. Malaria prophylaxis in sickle cell disease- a review. at <http://www.thecochranelibrary.com/userfiles/ccoch/file/CD003489.pdf>

7. Gaston, M. H. *et al.* Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. *N. Engl. J. Med.* **314,** 1593–9 (1986).

8. Okpala, I. The management of crisis in sickle cell disease. *Eur. J. Haematol.* **60,** 1–6 (1998).

9. *Practical Management of Haemoglobinopathies*. (Blackwell Publishing Ltd, 2004). doi:10.1002/9780470988398

10. The Management of Sickle Cell Disease. at <http://www.nhlbi.nih.gov/health/prof/blood/sickle/sc_mngt.pdf>

11. Rosse, W. F. *et al.* Transfusion and alloimmunization in sickle cell disease. The Cooperative Study of Sickle Cell Disease. *Blood* **76,** 1431–7 (1990).

12. Redwood, A. M. Climate and painful crisis of sickle-cell. (1976).

13. Koshy, M., Burd, L., Wallace, D., Moawad, A. & Baron, J. Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperative study. *N. Engl. J. Med.* **319,** 1447–52 (1988).

14. Dunbar, L. N., Coleman Brown, L., Rivera, D. R., Hartzema, A. G. & Lottenberg, R. Transfusion practices in the management of sickle cell disease: a survey of Florida hematologists/oncologists. *ISRN Hematol.* **2012,** 524513 (2012).

15. Consensus Development Panel, N. I. of H. Newborn screening for sickle cell disease and other hemoglobinopathies. *JAMA* **258,** 1205–1209 (1987).

16. Vichinsky, E., Hurst, D., Earles, A., Kleman, K. & Lubin, B. Newborn screening for sickle cell disease: effect on mortality. *Pediatrics* **81,** 749–55 (1988).

17. Davis, H., Schoendorf, K. C., Gergen, P. J. & Moore, R. M. National trends in the mortality of children with sickle cell disease, 1968 through 1992. *Am. J. Public Health* **87,** 1317–22

(1997).

18. Genetic course manual in sickle cell Disorder: Edited by Professor O.O.Akinyanju, Dr.O.Oluwatuyi, Mrs Ayo Otaigbe

19. Adegoke, S. A., Kuteyi, E. A. J. A. J. o. P. H. C., & Medicine, F. (2012). Psychosocial burden of sickle cell disease on the family, Nigeria. *4*(1), 1-6.

20. Anie, K. A. J. B. j. o. h. (2005). Psychological complications in sickle cell disease. *129*(6), 723-729.

21. Broome, M., Maikler, V., Kelber, S., Bailey, P., & Lea, G. J. J. o. N. B. N. A. J. (2001). An intervention to increase coping and reduce health care utilization for school-age children and adolescents with sickle cell disease. *12*(2), 6-14.

22. Callinan, C. E., Neuman, M. D., Lacy, K. E., Gabison, C., & Ashburn, M. A. J. T. J. o. P. (2017). The initiation of chronic opioids: a survey of chronic pain patients. *18*(4), 360-365.

23. Ilesanmi, O. O. (2010). Pathological basis of symptoms and crises in sickle cell disorder: implications for counseling and psychotherapy. *Journal of Hematology reports, 2*(1), e2.

24. Ilesanmi, O. O. (2013). Sickle Cell Disease (SCD) and Stem Cell Therapy (SCT): Implications for Psychotherapy and Genetic Counselling in Africa. In *Innovations in Stem Cell Transplantation*: IntechOpen.

25. Ilesanmi, O. O. (2014). Gender Differences in SCD Crises: Implications for Genetic Counselling and Psychotherapy. *Journal of International Journal of Information*

26. *Education Technology, 4*(2), 215.

27. Kaslow, N. J., Collins, M. H., Rashid, F. L., Baskin, M. L., Griffith, J. R., Hollins, L., . . . Health. (2000). The efficacy of a pilot family psychoeducational intervention for pediatric sickle cell disease (SCD). *18*(4), 381.

28. National Academies of Sciences, E., & Medicine. (2020). Addressing sickle cell disease: a strategic plan and blueprint for action.

29. Omoigui, S. Sickle Cell Pain Crisis: Clinical Guidelines for the Use of Oxygen.

30. Organization, W. H. (2006). World Health Assembly, 59. Sickle-cell anaemia: report by the secretariat. *Journal of World Health Organization*.

31. Organization, W. H. (2011). *Psychological first aid: Guide for field workers*: World Health Organization.

32. Ruta, N. S., & Ballas, S. K. J. P. M. (2016). The opioid drug epidemic and sickle cell disease: guilt by association. *17*(10), 1793-1798.

33. Stephen, N., Nden, N., Gusen, N. J., Kumzhi, P. R., Gaknung, B., Auta, D. A., Nanvyat, N. (2018). Prevalence of sickle cell disease among children attending plateau specialist hospital, Jos, Nigeria.

34. Thomas, V. J. N. J. I. J. o. P. N. (2000). Cognitive behavioural therapy in pain management for

sickle cell disease. *6*(9), 434-442.

35. Singh et al, Blood Advances, 2021. 10.1182? blood advances.2020003741.

APPENDICES

Appendix 1:

LIST OF CONTRIBUTORS TO THE DEVELOPMENT OF THE FIRST EDITION OF THE NATIONAL GUIDELINE FOR THE CONTROL AND MANAGEMENT OF SICKLE CELL DISEASE

S/N	Name	Designation	Organization
	Top Management Team		
1	Prof. C.O. Onyebuchi Chukwu	Honourable Minister	Federal Ministry of Health
2	Dr Khaliru Alhassan	Honourable Minister of State	Federal Ministry of Health
3	Dr Muhammad Ali Pate	Former Honourable Minister of State	Federal Ministry of Health
4	Mr Linus Awute	Permanent Secretary	Federal Ministry of Health
5	Amb. Sani Bala	Former Permanent Secretary	Federal Ministry of Health
6	Mrs Fatima Bamidele	Former Permanent Secretary	Federal Ministry of Health
7	Dr Bridget Okoeguale	Director of Public Health	Federal Ministry of Health
8	Dr Mansur Kabir	Former Director of Public Health	Federal Ministry of Health
9	Dr Jacintha E. George	Former National Coordinator, NCDs Control Division	Federal Ministry of Health
	Expert Resource Persons		
10	Prof. Olu Akinyanju	Chairman	Sickle Cell Foundation of Nigeria
11	Prof. Iheanyi Okpala	Consultant Haematologist	University of Nigeria College of Medicine, Enugu.
12	Dr Obiageli. E. Nnodu	Consultant Haematologist	University of Abuja, Abuja

S/N	Name	Designation	Organization
13	Dr A.B. Oyesakin	Consultant Paediatrician	National Hospital, Abuja
14	Dr O. Oniyangi	Consultant Paediatician	National Hospital, Abuja
15	Dr Uduak Essen	Medical Officer	Federal Capital Territory, Health Secretariat, Abuja
16	Dr Franklin Osungwu	Clinician	National Institute for Pharmaceutical Research and Development (NIPRD)
17	Dr N.I. Ugwu	Consultant Haematologist	Federal Teaching Hospital, Abakaliki
18	Dr N.P. Udechukwu	Consultant Paediatician	Federal Teaching Hospital, Abakaliki
19	Dr R.N. Okwudiafor		Federal Medical Center, Ebute- Metta
20	Dr A.I. Girei	Consultant Haematologist	Federal Medical Center, Gombe
21	Pharm. Arinde	Pharmacist	Bond Chemical Industries
22	Pharm. Sanjo A. Oyeniyi	Pharmacist	Bond Chemical Industries
23	S.O. Adeyemo		
24	Dr Chinatu Ohiaeri	Consultant Paediatrician	Federal Medical Centre, Keffi
25	Dr Rui Gama Vaz	WHO Country Representative	WHO Country Office, Abuja
Other Contributors			
26	Dr Benard A. Bene	Desk Officer, SCD (NCDs Control Division	Federal Ministry of Health
27	Dr Alayo Sopekan	Former Desk Officer, SCD (NCDs Control Division)	Federal Ministry of Health
28	Mr Donald Ordu	Staff, NCDs Control Division	Federal Ministry of Health
29	Mrs Jummai J.C. Balami	Staff, NCDs Control Division	Federal Ministry of Health

S/N	Name	Designation	Organization
30	Mr Joseph O. Nwokocha	Staff, NCDs Control Division	Federal Ministry of Health
31	Mrs Nneka Etta	Staff, NCDs Control Division	Federal Ministry of Health
32	Dr Mangai T. Malau	Staff, NCDs Control Division	Federal Ministry of Health
33	Dr Jibrin B. Suleiman	Head, Coordinating Unit, Department of Public Health	Federal Ministry of Health
34	Dr Alison Abdullahi	Staff, NCDs Control Division	Federal Ministry of Health
35	Mrs Veronica S. Augustine	Staff, NCDs Control Division	Federal Ministry of Health
36	Mrs Fortune Udott	Staff, NCDs Control Division	Federal Ministry of Health
37	Mrs Bosede Kehinde	Staff, NCDs Control Division	Federal Ministry of Health
38	Mrs Amaka Omoyele	Staff, NCDs Control Division	Federal Ministry of Health
39	Miss Funmi Areola	Staff, NCDs Control Division	Federal Ministry of Health
40	Mrs Ngozi Nwosu	Staff, NCDs Control Division	Federal Ministry of Health
41	Mrs Helen Onah	Staff, NCDs Control Division	Federal Ministry of Health
42	Mr Badejo W. Rotimi	MDGs Office	Federal Ministry of Health
43	Mr Emmanuel C. Ibeku	Staff, Department of Public Health	Federal Ministry of Health
44	Miss Ezidwa Siddi	Youth Corps Member	Federal Ministry of Health

Appendix 2:

Sickle Cell Centers of Excellence Established by the Federal Ministry of Health

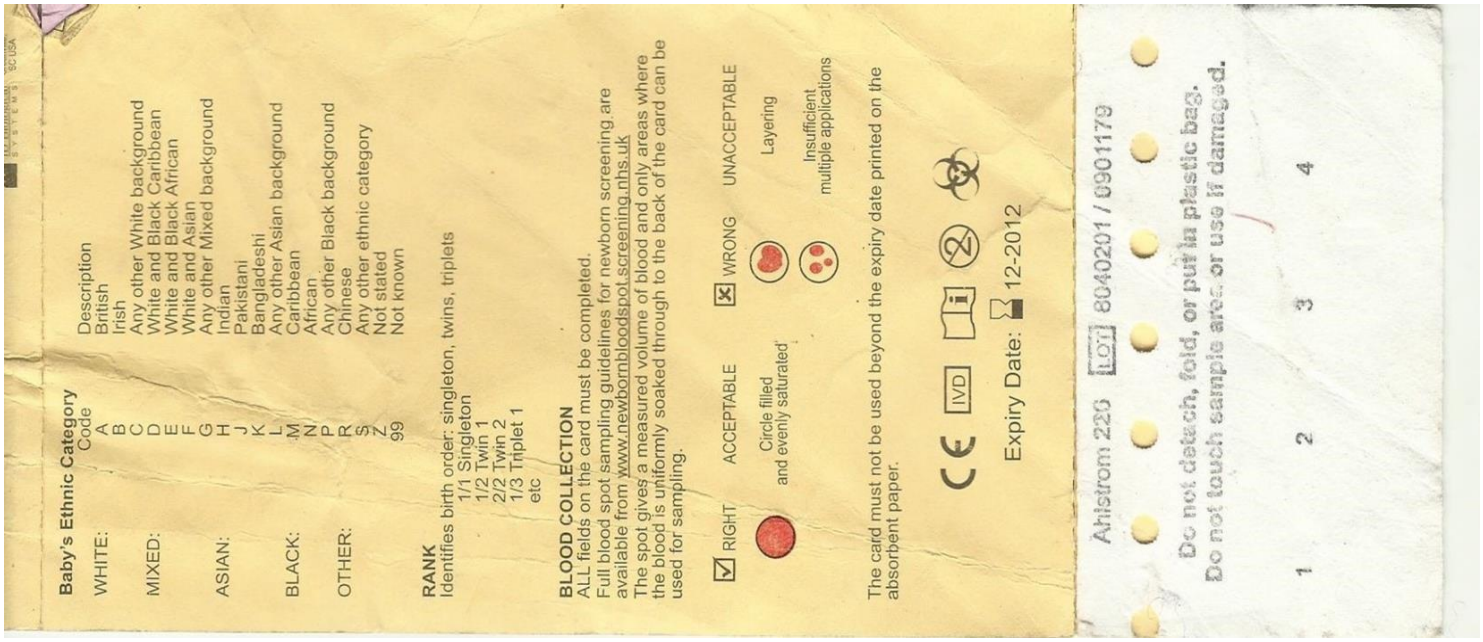
1. Federal Medical Center, Abakaliki, Ebonyi State.
2. Federal Medical Center, Birnin-Kebbi, Kebbi State.
3. Federal Medical Center, Ebute- Metta, Lagos State.
4. Federal Medical Center, Gombe, Gombe State.
5. Federal Medical Center, Keffi, Nasarawa State.
6. University of Benin Teaching Hospital, Benin.

Appendix 3:

A Picture of High Performance Liquid Chromatography (HPLC) Machine

Appendix 4:

Example of Sample Collection Card (Back page).



Baby's Ethnic Category

	Code	Description
WHITE:	A	British
	B	Irish
	C	Any other White background
MIXED:	D	White and Black Caribbean
	E	White and Black African
	F	White and Asian
	G	Any other Mixed background
ASIAN:	H	Indian
	J	Pakistani
	K	Bangladeshi
	L	Any other Asian background
BLACK:	M	Caribbean
	N	African
	P	Any other Black background
OTHER:	R	Chinese
	S	Any other ethnic category
	Z	Not stated
	99	Not known

RANK
Identifies birth order: singleton, twins, triplets
1/1 Singleton
1/2 Twin 1
2/2 Twin 2
1/3 Triplet 1
etc

BLOOD COLLECTION
ALL fields on the card must be completed.
Full blood spot sampling guidelines for newborn screening are available from www.newbornbloodspot.screening.nhs.uk
The spot gives a measured volume of blood and only areas where the blood is uniformly soaked through to the back of the card can be used for sampling.

☑ RIGHT ACCEPTABLE ☒ WRONG UNACCEPTABLE

Circle filled and evenly saturated

Layering

Insufficient multiple applications

The card must not be used beyond the expiry date printed on the absorbent paper.

CE IVD

Expiry Date: 12-2012

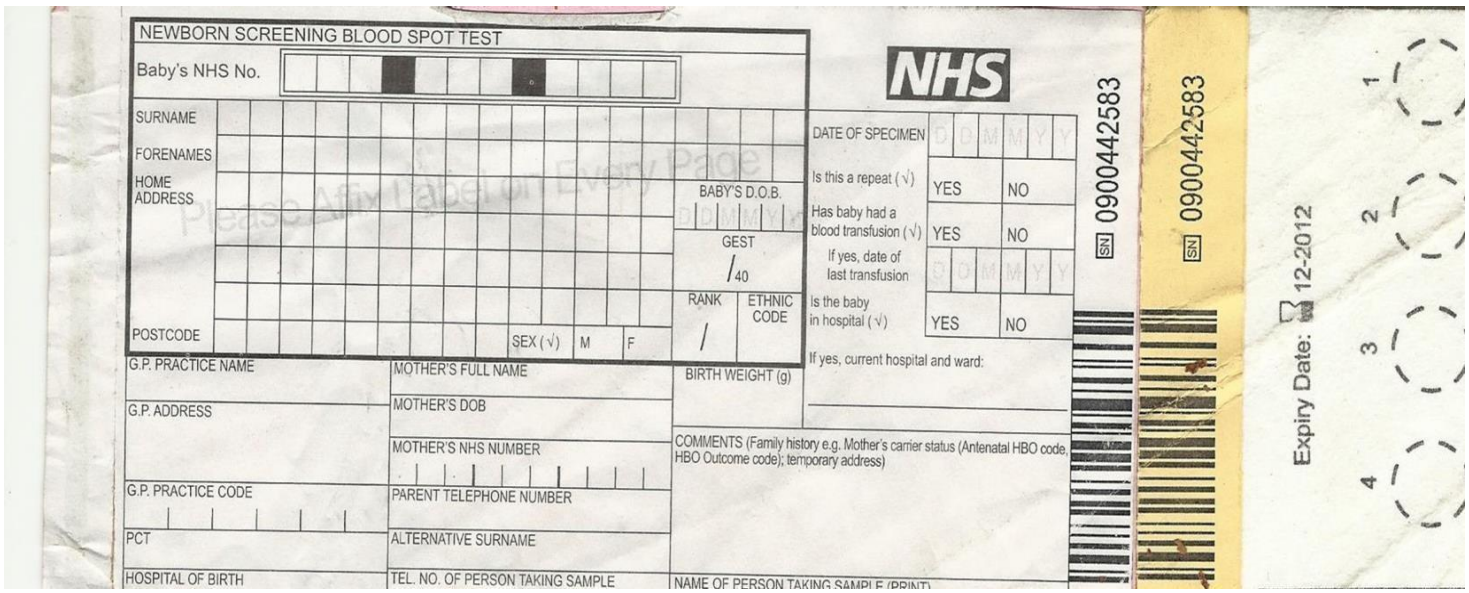
Ahlstrom 226 LOT 8040201 / 0901179

Do not detach, fold, or put in plastic bag.
Do not touch sample area or use if damaged.

1 2 3 4

Appendix 5:

Example of Sample Collection Card (Front page).



NEWBORN SCREENING BLOOD SPOT TEST

Baby's NHS No.

NHS

SURNAME

FORENAMES

HOME ADDRESS

POSTCODE

SEX (√) M F

BABY'S D.O.B. D D M M Y Y

GEST /40

RANK /

ETHNIC CODE

DATE OF SPECIMEN D D M M Y Y

Is this a repeat (√) YES NO

Has baby had a blood transfusion (√) YES NO

If yes, date of last transfusion D D M M Y Y

Is the baby in hospital (√) YES NO

If yes, current hospital and ward:

G.P. PRACTICE NAME

G.P. ADDRESS

G.P. PRACTICE CODE

PCT

HOSPITAL OF BIRTH

MOTHER'S FULL NAME

MOTHER'S DOB

MOTHER'S NHS NUMBER

PARENT TELEPHONE NUMBER

ALTERNATIVE SURNAME

TEL. NO. OF PERSON TAKING SAMPLE

BIRTH WEIGHT (g)

COMMENTS (Family history e.g. Mother's carrier status (Antenatal HBO code, HBO Outcome code); temporary address)

NAME OF PERSON TAKING SAMPLE (PRINT)

SN 0900442583

SN 0900442583

Expiry Date: 12-2012

1 2 3 4