



FEDERAL MINISTRY OF
HEALTH

Meeting the Health Needs of all Nigerians

NATIONAL GUIDELINE FOR THE CONTROL AND MANAGEMENT OF SICKLE CELL DISEASE



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This guideline shall be updated periodically.

Comments and suggestions concerning its contents are encouraged and should be sent to:

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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 undermining the attainment of the Millennium Development Goals (MDGs) 4, 5 and 6. SCD is particularly associated with increased maternal, neonatal, infant and child mortality. It is also occasionally associated with HIV and viral hepatitis (mainly B and C) infections due to frequent blood transfusion. 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, depression and other psychosocial challenges.

Concerned about the enormous challenges caused by SCD and in line with President Goodluck Jonathan's transformation agenda, the Federal Ministry of Health (FMOH) in collaboration with the MDG office in 2011 and 2012 empowered six Federal Medical Centers in all the six geopolitical zones in the country to run dedicated clinics and programmes for the management and control of SCD.

Furthermore, the publication of this guideline shows government's continuous commitment to reduce the burden of SCD as it is essential that affected individuals receive appropriate clinical interventions in all healthcare facilities nationwide.

I therefore encourage all healthcare facilities to take advantage of this opportunity to improve their standard of care for SCD individuals thereby improving the management and control of SCD in Nigeria and thus contribute to our efforts in bringing hope and succor to those affected by this disease.



Prof. C. O. Onyebuchi Chukwu

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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 HbS β -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 management.

Nigeria, being the most populous country in 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.

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 expected to provide uniformity and standardized procedure in the control and management of SCD in all health facilities across the country.

Hence, it is our earnest desire that this document will form the foundation for improving the standard of care for SCD patients in all our healthcare facilities across the country.

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ACKNOWLEDGEMENT

We sincerely appreciate the team of stakeholders, including my predecessor National Coordinators of the Non-Communicable Disease Division, who contributed immensely to the development of this document. The excellent team was made up of the Department of Public Health (NCD Division – as the secretariat); line Departments such as Family Health, Hospital Services, Planning, Research & Statistics/MDGs etc.; Academia; Research Institution (NIPRID); Professional Bodies (Nigerian SCD Network, Sickle Cell Foundation Nigeria); Civil Society Organizations; and the private sector (Pharmaceutical) to mention but a few. A special thanks to Professor John Walley (Clinical Professor of International Public Health and Co-Director COMDIS-Health Service Delivery Research Programme, Nuffield Centre for International Health and Development, Leeds Institute of Health Sciences, University of Leeds, United Kingdom) for his wise counsel.

We sincerely hope that the same spirit of partnership displayed during the development of this document 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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CONTENTS

FOREWORD	III
PREFACE.....	IV
ACKNOWLEDGEMENT	V
LIST OF CONTRIBUTORS TO THE DEVELOPMENT OF THE NATIONAL GUIDELINE FOR THE CONTROL AND MANAGEMENT OF SICKLE CELL DISEASE	VI
LIST OF TABLES	XIV
LIST OF FIGURES.....	XIV
LIST OF ACRONYMS	XIV
CHAPTER 1.....	1
BACKGROUND.....	1
1.1 Definition.....	1
1.2 Forms of Sickle Cell Disease.....	1
1.3 The Burden of Sickle Cell Disease	1
1.4 The Rationale for a National Guideline for the Control and Management of Sickle Cell Disease.....	1
CHAPTER 2.....	3
DIAGNOSIS OF SICKLE CELL DISEASE.....	3
2.1 Clinical Presentation of Sickle Cell Disease.....	3
2.2 Laboratory Diagnosis of Sickle Cell Disease	3
2.2.1 Sickling Test	4
2.2.2 Solubility Test.....	5
2.2.3 Haemoglobin Electrophoresis (HE)	6
2.2.5 High-Performance Liquid Chromatography (HPLC).....	9
2.2.6 Isoelectric Focusing (IEF)	9
2.2.7 Other Tests.....	10
2.3 Quality Assurance and Laboratory Standards.....	11
2.3.1 Quality Control.....	11

2.3.2	Quality Assessment of a Laboratory.....	12
CHAPTER 3	13
MANAGEMENT OF ACUTE COMPLICATIONS IN SICKLE CELL DISEASE	13
3.1	Introduction.....	13
3.2	Acute Clinical Presentations.....	13
3.2.1	Sickle Cell Crisis.....	13
3.2.2	Priapism.....	19
3.3.3	Acute Chest Syndrome.....	21
3.3.4	Stroke Secondary to Sickle Cell Disease.....	22
CHAPTER 4	25
SPECIAL SITUATIONS	25
4.1	Hydroxyurea Therapy for Sickle Cell Disease.....	25
4.1.1	Suggested Indications for Hydroxyurea Therapy in Nigeria.....	25
4.1.2	Contraindications.....	25
4.1.3	How Hydroxyurea Works in Sickle Cell Disease.....	26
4.1.4	Dosage of Hydroxyurea.....	26
4.2	Prophylaxis and Antimicrobial Therapy.....	26
4.2.1	Malaria Prophylaxis.....	26
4.2.2	Prophylactic Antibiotics.....	27
4.2.3	Therapeutic Antibiotics.....	27
4.3	Management of Osteomyelitis in Sickle Cell Disease.....	27
4.3.1	Investigations that Help to Detect Acute Osteomyelitis.....	28
4.3.2	Treatment of Osteomyelitis.....	28
4.4	Blood Transfusion in Sickle Cell Disease.....	28
4.4.1	Simple (Top-Up) Blood Transfusion.....	28
4.4.2	Exchange Blood Transfusion.....	29
	Relative Indications for Exchange Blood Transfusion:.....	29

4.5	Peri-Operative Management of Patients with Sickle Cell Disease.....	32
4.5.1	Using General Anaesthesia.....	33
4.5.2	Blood Transfusion.....	34
4.5.3	Oxygen Therapy.....	34
4.5.4	Hydration.....	34
4.5.5	Hypothermia.....	34
4.5.6	Sickle Cell Trait.....	35
CHAPTER 5.....		36
SICKLE CELL DISEASE AND PREGNANCY.....		36
5.1	Introduction.....	36
5.2	Effects of Sickle Cell Disease on Pregnancy.....	36
5.3	Documented Complications of Pregnancy with Sickle Cell Disease	37
5.4	Multidisciplinary Team Approach to the Management of Sickle Cell Disease in Pregnancy ...	37
5.5	Pre-Conception Counselling.....	38
5.6	Pre-Natal Diagnosis	39
5.7	At Booking.....	39
5.8	Ante-Natal Care	39
5.9	Prophylactic Transfusion	40
5.10	Admission Criteria.....	40
5.11	Discharge Criteria following Treatment for Sickle Cell Crisis	40
5.12	Intrapartum.....	40
5.13	Postpartum.....	41
5.14	Contraception.....	41
CHAPTER 6.....		42
MANAGEMENT OF CHRONIC COMPLICATIONS OF SICKLE CELL DISEASE.....		42
6.1	Introduction.....	42
6.1.1	Osteonecrosis (Avascular Necrosis).....	42

6.2	Management of Ocular Complications in Sickle Cell Disease.....	43
6.3	Management of Renal Complications in Sickle Cell Disease.....	43
6.4	Management of Chronic Leg Ulceration in Sickle Cell Disease	44
CHAPTER 7.....		46
CARE IN STEADY STATE OF SICKLE CELL DISEASE		46
7.1	Introduction.....	46
7.2	Routine Prophylactic Measures	46
7.2.1	Malaria Prevention	46
7.2.2	Prevention of Anaemia.....	46
7.2.3	Prevention of Infections.....	46
7.3	Growth and Development Monitoring in children with Sickle Cell Disease.....	48
7.4	Home Care in Sickle Cell Disease.....	48
7.4.1	Nutrition.....	48
7.4.2	Recognition of Early Features of Crises in Sickle Cell Disease	48
7.5	Recommended Regular Clinical Assessment of Sickle Cell Disease Patients in Steady State at the Out-Patient Clinic	48
7.5.1	Three to Six (3-6) Monthly.....	48
7.5.2	Annually/Bi-annually	49
7.5.3	Meeting.....	49
CHAPTER 8.....		50
GENETIC COUNSELING AND TESTING IN SICKLE CELL DISEASE.....		50
8.1	Introduction.....	50
8.2	Why Genetic Counseling and Testing in Sickle Cell Disease?	50
8.3	Procedures /Counseling Process.....	50
8.4	Challenges of Counselling in Sickle Cell Disease	51
CHAPTER 9.....		52
NEWBORN SCREENING AND DIAGNOSIS IN SICKLE CELL DISEASE		52
9.1	Introduction.....	52

9.2	Steps in Collection of Sample.....	52
9.3	Movement and Transportation of Collected Samples.....	53
9.4	Laboratory Testing of Newborn Blood Samples for Haemoglobinopathy Screening	54
9.5	Protocol for Processing Laboratory Samples	54
9.5.1	Entry Point.....	54
9.5.2	In the Laboratory.....	54
9.5.3	Reporting	55
9.5.4	Communicating and Release of Result	55
9.5	Database.....	56
9.5.1	Objectives.....	56
9.5.2	Plan	56
9.5.3	Information to be put on the form for screening.....	57
9.6	Coverage of Newborn Screening	57
APPENDICES.....		59
Appendix 1: Sickle Cell Centres Established by the Federal Ministry of Health		59
Appendix 2: Example of Sample Collection Card		59
Appendix 3: A Picture of High Performance Liquid Chromatography Machine		60
REFERENCES.....		61

LIST OF TABLES

Table 1	Initial Treatment of Patient in Sickle Cell Crisis
Table 2	Investigations That Influence Immediate Management of Sickle Cell Crisis
Table 3	Fluid Management in Painful Crisis
Table 4	Blood Transfusion in Painful Crisis
Table 5	Treatment of Acute Pain in Sickle Cell Disease
Table 6	Clinical Features of Acute Chest Syndrome
Table 7	Benefits, Side-effects & Potential Risks of Hydroxyurea Therapy
Table 8	Immunization Schedule 1
Table 9	Immunization Schedule 2

LIST OF FIGURES

Figure 1	Algorithm for Definitive Laboratory Diagnosis of Sickle Cell Disease
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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

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 gene.

1.2 Forms of Sickle Cell Disease

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

If a person inherited two sickle haemoglobins (HbS) from both parents, the individual has HbSS; while a person who 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 from one parent and another haemoglobin variant (Hb β -thalassaemia) from another parent has HbS β -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

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 the 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 various

therapeutic procedures; to facilitate uniformity and standardization of care across different disciplines. Such guidelines and protocols should be regularly revised and updated in line with developments in clinical practice and findings from scientific research.

CHAPTER 2

DIAGNOSIS OF SICKLE CELL DISEASE

2.1 Clinical Presentation of Sickle Cell Disease

Patients with Sickle Cell Disease (SCD) have inherited genes which 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) 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 hospitalisations 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 is dependent on the demonstration of haemoglobin 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:

- Sickling test
- Solubility test
- Haemoglobin electrophoresis (either in alkaline or acidic pH)
- Blood film
- High Performance Liquid Chromatography (HPLC)
- Isoelectric Focusing (IEF)
- Others such as Kleihauer-Betke Test and Molecular Technique

2.2.1 Sickling Test

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

Principle: This demonstrates 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 newborn
- b) Could miss other hemoglobinopathies

2.2.2 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°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 newborn
- b) Could miss other hemoglobinopathies
- c) It requires an unrelated second line method for confirmation of result.

2.2.3 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. The final position of a haemoglobin type depends on the pH of the medium and the charge of the haemoglobin molecule. The medium for electrophoresis at acidic (low pH) is the agar gel, while the alkaline medium is **cellulose acetate**. Electrophoresis is erroneously called 'genotype'. In actual fact it is the description of phenotype. The zone of migration of Hb S in an alkaline medium may coincide with that of Haemoglobin D, E, and G in electrophoresis 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 and solubility test (or sickling test) is adopted.

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 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 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 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) Electrophoresis ‘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 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 electrophoresis ‘run’ for 10 minutes.

- Excess fluid is blotted off using filter paper
- The strip is dried face downwards
- All samples that show 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 same conditions
- Haemoglobin-S will give a positive solubility test, while other haemoglobin types will give 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 positive results
- c) It requires an unrelated second line method for confirmation of result.

2.2.4 Blood Film

This plays a dual role of demonstrating sickle cells and features of complications of sickle cell disorder such as, megaloblastic anaemia, 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° 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 parasite.

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:

Requires higher level manpower.

2.2.5 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 S β^+ thalassaemia 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 newborn 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 haemoglobin which can make interpretation difficult
- e) It requires an unrelated second line method for confirmation of result.

2.2.6 Isoelectric Focusing (IEF)

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

Advantages of IEF:

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

Limitations of IEF:

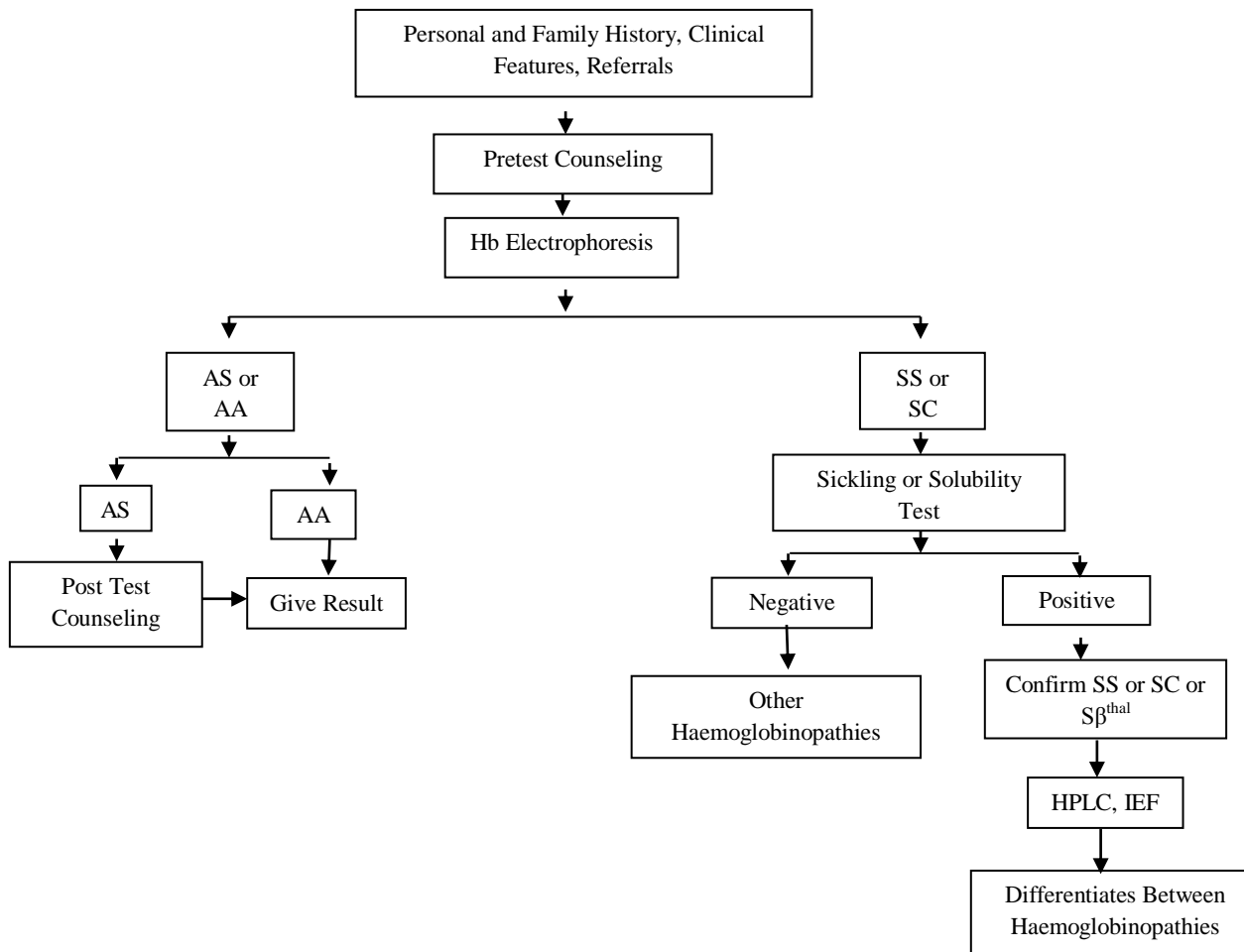
- a) Very expensive (equipment, maintenance and testing)
- b) Requires electricity
- c) Requires optimal room temperature to function accurately
- d) It separates glycosylated and other derivative forms of haemoglobin which can make interpretation difficult.
- e) It requires unrelated second line method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

2.2.7 Other Tests

- a) **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.
- b) **Molecular Technique** (mutation detection and sequencing analysis): Used predominantly for pre-natal diagnosis.

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

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



Note: This applies at all levels of care except in Primary healthcare facilities where Hb electrophoresis testing is not feasible.

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 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 equipments 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 HbS β -thal). This section of the guideline is focused on the clinical care of people living with the condition.

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
- Priapism
- Acute Chest Syndrome
- Stroke

3.2.1 Sickle Cell Crisis

This refers to a worsening, over a short period of time, 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 a number of 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 O₂ 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 <i>if necessary</i>
Address specific clinical problems <i>e.g. stroke, acute chest syndrome, priapism.</i>

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) Sequestration crisis: results from trapping of red blood cells in the spleen or liver
- c) Aplastic crisis: acute reduction of red cell production in the marrow caused by parvovirus B19.

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: <ul style="list-style-type: none"> • Dihydrocodeine tablets 30 mg 4 hrly plus • Paracetamol 1g 4 hrly 	Immediate-release oral formulation of stronger opiate e.g. morphine 4 hrly
	Children: <ul style="list-style-type: none"> • Paracetamol 20mg/kg 4 to 6hrly with/without Ibuprofen 10mg/kg 8hrly Or diclofenac 1mg/kg 8hrly • Dihydrocodeine 1mg/kg 8hrly 	
Moderate/Severe	Adult: <ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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
	<p>Children:</p> <ul style="list-style-type: none"> • 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 opioids • **Inj tramadol 100mg 1-2 hrs after NSAIDs 	

***This is necessary so as 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: prochlorperazine 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.

B. Sequestration Crisis

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 HbS β -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) ‘Hypovolaemic’ 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

- 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.

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.

C. Aplastic Crisis

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.

3.2.2 Priapism

This refers to a prolonged painful penile erection, not associated with sexual stimulation.

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.

Complications:

- a) Erectile dysfunction
- b) 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) Give 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
- b) 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
- c) 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) Urologists should aspirate and irrigate corpora cavernosa with 6-10 mg of injectables 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

- d) If repeat irrigation of cavernosa with etilefrine does not lead to detumescence after 1 hour, 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 Chest Syndrome

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. The 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 lung
	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 A₂ (sPLA₂) 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 A₂ and in ACS serum CRP is usually $\geq 5\text{mg/L}$*
- *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.

3.3.4 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 $>200\text{cm/s}$ 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 10⁹/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.*

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.

Prevention of Primary Stroke in SCD:

- a) In children ≤ 16 yrs 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.

In an attempt 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) ≥ 5 crises per year
- b) 3-4 crises per year AND either neutrophil count $\geq 10 \times 10^9 /L$ or platelet count $\geq 500 \times 10^9 /L$ 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 $< 2 \times 10^9/L$
 - Platelet $< 100 \times 10^9/L$
 - Reticulocytes (young RBCs) $< 80 \times 10^9/L$
- c) Liver Disease
- d) Kidney Failure

Note: *People on Hydroxyurea therapy should be monitored 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 SCD⁴

- 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.

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 osteomyelitis 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 as 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 disease⁵. 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 erythrocytapheresis 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 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**

The features of Citrate toxicity are:

- Hypocalcaemia – circumoral muscle twitching and paraesthesia
- Nausea, vomiting
- Chills
- Cardiac arrhythmias
- 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 suffice⁷ SCD patients are prone to red cell antibody formation⁸. 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 2nd – 4th 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 crisis⁹ 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
- b) 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 biomarkers 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

Problems of the musculoskeletal system are prominent in the life of the individual with sickle cell disease. Many affected individuals are living longer due to improved medical care and therefore present with chronic bone and joint conditions that are peculiar to this disease.

Chronic orthopaedic manifestations of SCD include:

- a) Pyogenic infections (chronic osteomyelitis)
- b) Bone marrow hyperplasia
- c) Pathological fractures
- d) Avascular necrosis of the femoral head arising in the 2nd decade of life due to blood vessel thrombosis and infarctions.

Note: *Effective management requires an understanding of the disease pathology, early recognition of clinical manifestations, knowledge of the potential medical and surgical complications and a multidisciplinary approach.*

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

Treatment:

Can be Non-Operative and/or Operative.

- a) Non-Operative:
 - Pain management with the use of Paracetamol, Non-Steroidal Anti-Inflammatory Agents and/or Opiates such as Codeine and Tramadol.

b) Operative:

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

6.2 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:

- a) Swelling of the eyelid
- b) Protrusion of the eyeball
- c) Droopy eyelids
- d) Ocular redness
- e) Yellowness of the eyes
- f) Crossed eyes
- g) Ocular aches
- h) Floaters (appearance of dots or cobwebs which move along with patient's gaze)
- i) Flashes of light
- j) 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.

6.3 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:

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

- c) 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
- d) 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.*

6.4 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.

Clinical Features:

- a) Typical ulcerations are situated around the medial or lateral malleolus of one or both ankles
- b) It arises spontaneously, although a history of preceding trauma may occasionally be obtained from the patient
- c) Healing is very slow and recurrence or breakdown of healed ulcers is very common.

Treatment:

- a) Daily wound dressing
- b) Rest and elevate the affected limb
- c) Treat any associated infection
- d) Autologous skin graft.

Factors that Promote Healing Leg Ulcers:

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

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.

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 health care 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 measure that can help reduce the frequency of malaria:

- a) Anti-malarial prophylaxis:
 - Proguanil tablets 100-200 mg daily for > 6 years; 25mg for < 1 year; 50mg for 1- 3 years; 20mg to 100mg for 3-6 years
- b) Environmental control:
 - In door 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

Prophylactic Oral Penicillin V:

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

Immunizations:

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 Conjugate 13 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 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.

Table 9: Immunization Schedule 2

Immunization	When
BCG	At birth
OPV ₀	At birth
OPV ₁ +Penta 1	6 weeks
OPV ₂ +Penta 2	10 weeks
OPV ₃ +Penta 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 Conjugate 13 Valent Vaccine from 6 weeks (monthly x 3 doses) and a booster at 12 months, followed by Pneumococcal Polysaccharide 23 Valent

Immunization	When
	Vaccine from 2 years with 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 1-5 years.

The weight and height should be plotted on the **Road to Health Chart**. Parents/Caregivers should be educated that the children may have reduced weight and height when compared with their peers, but that they may catch up in growth especially during adolescence.

7.4 Home Care in Sickle Cell Disease

7.4.1 Nutrition

- a) Exclusive breast feeding for 6 months should be encouraged
- b) The children should have complementary feeding from 6 months with proteins (liver, meat, fish and beans) fruits, potatoes, yam and green leafy vegetables.

7.4.2 Recognition of Early Features of Crises in Sickle Cell Disease

- a) Caregivers should be taught how to recognize pallor (whiteness of the palms, soles of feet, skin and lips) and checking the conjunctivae for yellowish discolouration and abdomen for splenic enlargement
- b) They should also be taught to properly assess severity of pain and early signs of ill health such as: listlessness, refusal to play and fever.
- c) 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 Three to Six (3-6) Monthly

- a) History indicative of specific features of sickle cell disease, such as priapism
- b) Physical examination and vital signs
- c) Laboratory investigations as follows:
 - Complete/Full Blood Count

- Liver Function Tests
- Total plasma protein with albumin globulin fraction
- Kidney Function Test

7.5.2 Annually/Bi-annually

- a) Echocardiography to detect pulmonary hypertension
- b) Ophthalmology review
- c) Dental review
- d) ENT review
- e) Transcranial Doppler Ultrasonography to identify people at risk of stroke from 2-16 years.

7.5.3 Meeting

Patients group/individual patient meeting with carers who provide various components of holistic care, such as counselling, information about sickle cell disease, 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 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 come to terms with and cope better with the disorder.

8.2 Why Genetic Counseling and Testing in Sickle Cell Disease?

- a) Genetic Counselling and Testing helps to identify and provide accurate information to affected individuals and family members about the condition and how it is passed , verbally and through IEC materials
- b) It is essential in tactfully but firmly dispelling myths and misinformation held by the client, family members and community about the disorder
- c) It ensures that the affected person understands the probable clinical course and treatment needs
- d) It informs the client about existing facilities for health and social care and provides a referral where necessary
- e) It provides the client with a spectrum of careers that are compatible with living with sickle cell disorder
- f) It provides the opportunity to encourage affected clients and their family members by referring them to successful role models living with SCD.

8.3 Procedures /Counseling Process

- a) A counseling session should be planned to ensure maximum comfort, minimal interruption and distractions and to dispel fear, anger, or confusion from the mind of the affected individuals and their family members
- b) The attitude of the counselor should be friendly, empathic and not make the affected person feel looked down upon
- c) Counseling should be provided by trained health care workers.

8.4 Challenges of Counselling in Sickle Cell Disease

- a) Owing to the large number of people groups, languages and diverse terrain in the country, counseling can be challenging
- b) To ensure that clients understand information presented to them, counseling should be done in local languages without losing the essential facts.

CHAPTER 9

NEWBORN SCREENING AND DIAGNOSIS IN SICKLE CELL DISEASE

9.1 Introduction

According to the 1990/92 National Survey on NCDs, 23.04% of Nigerians have the sickle cell trait; while in 2008, the World Health Organization (WHO) reported that an estimated 150,000 babies are born annually in Nigeria with SCD. 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 done at birth or at the neonatal period to enhance early detection of sickle cell haemoglobin. Experiences from developed countries have shown significant reduction in mortality in individuals affected by SCD when they are identified at birth.^{12, 13, 14} Such individuals are enrolled in a comprehensive care (prophylaxis for infections, prevention and screening for stroke, monitoring and treatment of complications). Therefore there is a need to have a multicentre approach to NBS. The major objectives of newborn screening are to: identify index cases; determine patterns of phenotypes across the country; and allow early intervention.

9.2 Steps in Collection of Sample

Newborn Screening should be done at birth or neonatal period after counseling the parents and obtaining their consent. The machines (Variant NBS High Profile Liquid Chromatography System) currently available in each of the six SCD centers can detect SCD in neonates and infants.

Materials:

- a) Disposable gloves
- b) Sterile lancets
- c) Methylated spirit swabs
- d) Labeled Guthrie cards (Baby's name, DOB, gender; 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 from the parent (usually the mother)
- b) Sample is collected through heel prick by the birth attendant as soon as possible after birth as opposed to cord sample. The heel of the newborn baby is gently massaged, and side of the heel is pricked with a disposable sterile lancet applying aseptic technique
- c) Put the blood on all the spots on the Guthrie card or absorbent paper
- d) Apply dry swab to the pricked area to stop the bleeding
- e) Allow the Guthrie card to dry and stack at the appropriate place
- f) Send samples to reference centers equipped with NBS machine for analysis
- g) When using absorbent paper to collect sample, the following information are required:
 - Baby's age (to be captured on a separate sheet)
 - Baby's name and DOB on the absorbent paper
 - Date of sample collection
 - Mother's/father's name
 - Contact/mobile number of parent
 - Parents' genotype if known.

9.3 Movement and Transportation of Collected Samples

- a) Collection of samples will be done at maternity units in each town/village
- b) The collected sample is moved by a designated person to the collection centre at the LGA the same day (say by 2pm) and then moved to the State capital also on the same day (say by 4-5pm)
- c) The sample will be picked from the terminus by a focal person at a designated centre (which should be open till 8pm) in the State capital
- d) These samples will then be moved to the zonal NBS centre by courier service or private transport service to be picked by staff of the NBS centre
- e) Samples must be transported in waterproof/tight package using standard operating protocols
- f) The same courier service will return the results (hard copies) as soon as they are ready
- g) In each maternity unit, one trusted health worker should be dedicated to receiving results electronically. If this is not possible, then there should be one at the LG level/township level.

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.*

9.4 Laboratory Testing of Newborn Blood Samples for Haemoglobinopathy Screening

Haemoglobin electrophoresis using cellulose acetate has been the usual method for the diagnosis of haemoglobinopathies in this country. This method is plagued with limitations such as:

- a) Waiting until the child is six month old, because the method is not sensitive enough
- b) Poor reproducibility
- c) Method is cumbersome
- d) It is labour intensive
- e) Not suitable for large scale screening
- f) It utilizes wet sampling which imposes logistic issues for transportation of samples
- g) Method does not easily quantify haemoglobins.

The high performance liquid chromatography (HPLC) systems should therefore be used to take care of the short comings of the above method. HPLC is preferred to iso-electric focusing (IEF) because it:

- a) Is user friendly
- b) Has high through-put, i.e can process many samples in a unit of time, such as 1 day.
- c) Is more precise, fully automated and reliable
- d) Is less operator dependent
- e) More cost effective.

9.5 Protocol for Processing Laboratory Samples

- Entry point
- In the laboratory
- Reporting
- Communicating and release of results

9.5.1 Entry Point

- a) Check whether samples were correctly applied on the sample collection card (SCC).
- b) Verify the completeness of the information on the SCC.
- c) Input relevant patient data into a register.
- d) Send SCC to the laboratory for analysis.

9.5.2 In the Laboratory

- a) Reconfirm that the sample collection is appropriate
- b) Set up a work list for a particular run

- c) Punch out the best blot into the wells of a microplate in an order that correlates with the work list
- d) Apply distilled water to the wells and allow to stand for at least 10 minutes
- e) Place the microplates on a plate shaker for about 3 minutes
- f) Place the microplates into the sampling station of the HPLC machine and commence the runs (analysis of each sample should take approximately 3 minutes)
- g) Quality control protocols as defined for the system should be strictly adhered to by the operator/scientist
- h) Routine protocols for maintenance of the machine must be adhered to and summaries of these actions should be sent to and verified by the QA Officer
- i) The laboratory should participate in external QA Programmes.

Note: *Tests must be conducted by only trained personnel.*

9.5.3 Reporting

- a) Collation of Results
 - This should be done by the scientist on the bench within 24 hour of each run;
 - Hard copies of the results indicating the chromatogram and summary table should be sent to the specialist (i.e. Haematologist) for interpretation
- b) Interpretation
 - This should be done by a Haematologist
 - Interpretation should be based on acceptance criteria for HPLC (machine manual)
 - Results that meet the acceptance criteria should be signed out by the Haematologist for onward dispatch to the client
 - Results that do not meet the acceptance criteria should be returned to the scientist for re-run or other actions.

9.5.4 Communicating and Release of 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.

Steps in Communicating the Result:

- a) Revealing the results and discuss the implications of the result with the parents
- b) Observe reactions to the result
- c) Counselling and addressing concerns/myths and questions of the family
- d) Psychological Support
- e) Education and Provision of Education materials.

Counselling:

- 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 trained genetic counselor.*

9.5 Database**9.5.1 Objectives**

- a) To develop a database of patients screened at MDG Sickle Cell Centres and catchment areas
- b) To enrolment in a cohort for prospective surveillance
- c) To give interventions such as preventing complications.

9.5.2 Plan

- a) Start at the six existing MDGs Sickle Cell Centres
- b) Maintenance of registration of births (e.g. immunization template)
 - 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
- Birth order
- Results of SC screening
- Identification of those babies with SCD
- Type of sample taken
- Rank of birth
- c) Centre to input into FMOH website on Research & Statistics
- d) Need for software to manage the information input
- e) Input of data into the system by Health Information Officer in the centre
- f) Data manager at the NCD Control Programme to inter-phase with the FMOH website on Research & Statistics.

9.5.3 Information to be put on the form for screening

- a) DOB
- b) Age at screening
- c) Sex
- d) Baby's name
- e) Mother's name
- f) Place of delivery
 - State
 - LGA
 - Political ward
- g) Centre of registration
- h) Hospital number
- i) Current Address
- j) Contact phone number
- k) State of Origin
- l) Parents' genotype if known.

9.6 Coverage of Newborn Screening

The success of NBS depends on adequate coverage of communities with newborns getting tested. For this to happen, babies born in health facilities as well as those born at home should be tested.

A focal person at all levels (Ward, LGA, State and Federal) and within the health facilities should be responsible for advocacy and community mobilization for NBS. Babies born at home are best captured at immunization centers.

A register of all the screened children which highlights affected children with asterisks should be maintained and data transmitted quarterly through the reference centers to the NCDs Division of the FMOH.

Affected children shall be referred to relevant health centers for comprehensive care.

APPENDICES


Appendix 1: Sickle Cell Centres Established by the Federal Ministry of Health

- a) Federal Medical Center, Abakaliki, Ebonyi State.
- b) Federal Medical Center, Birnin-Kebbi, Kebbi State.
- c) Federal Medical Center, Ebute- Metta, Lagos State.
- d) Federal Medical Center, Gombe, Gombe State.
- e) Federal Medical Center, Keffi, Nasarawa State.
- f) Federal Medical Center, Yenagoa, Bayelsa State.

Appendix 2: Example of Sample Collection Card

- a) Front page

NEWBORN SCREENING BLOOD SPOT TEST									
Baby's NHS No. <input type="text"/>									
SURNAME		FORENAMES		HOME ADDRESS		BABY'S D.O.B.		DATE OF SPECIMEN	
						/ /		D D M M Y Y	
						GEST		Is this a repeat (✓)	
						/40		YES NO	
						RANK		Has baby had a blood transfusion (✓)	
						ETHNIC CODE		YES NO	
						/		If yes, date of last transfusion	
								S U M M Y Y	
POSTCODE		SEX (✓) M F						Is the baby in hospital (✓)	
								YES NO	
G.P. PRACTICE NAME		MOTHER'S FULL NAME		BIRTH WEIGHT (g)				If yes, current hospital and ward:	
G.P. ADDRESS		MOTHER'S DOB							
G.P. PRACTICE CODE		MOTHER'S NHS NUMBER		COMMENTS (Family history e.g. Mother's carrier status (Antenatal HBO code; HBO Outcome code); temporary address)					
PCT		PARENT TELEPHONE NUMBER							
HOSPITAL OF BIRTH		ALTERNATIVE SURNAME							
		TEL. NO. OF PERSON TAKING SAMPLE		NAME OF PERSON TAKING SAMPLE (PRINT)					



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Expiry Date: 12-2012

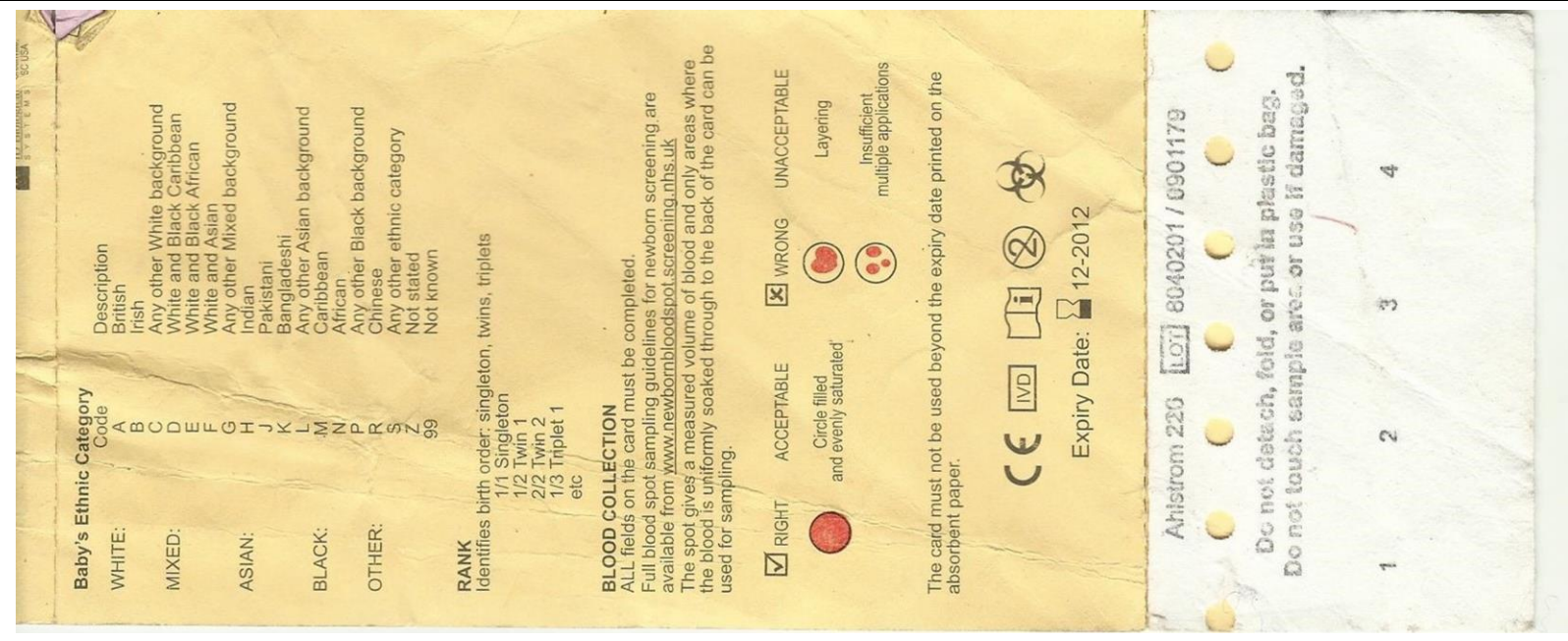
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b) Back cover



Appendix 3: A Picture of High Performance Liquid Chromatography Machine



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