SPARCo STANDARDS OF CARE FOR SICKLE CELL DISEASE IN SUB-SAHARAN AFRICA

Last Referral Hospital Standard Version

August, 2023

SPARCo
Sickle African
Research Consortium

SADaCC
Sickle Africa Data
Coordinating Centre

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Sickle Pan-African Research Consortium

SPARCO recommendations for the management of Sickle Cell Disease in Sub-Saharan Africa

FOREWORD

Sickle cell disease (SCD) is the commonest clinically significant haemoglobinopathy. It was first reported in literature in November 1910 by James Herrick when he saw “peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia”. (1) The sickling of RBCs contributes to Vaso-occlusion and intravascular hemolysis which leads to the symptomatology these patients present with. (2) They are at increased risk of coming with several complications which can lead to mortality if the appropriate management schedule is not instituted. The absence of a structured clinical management guideline can lead to lots of morbidity and mortality for the patient with SCD.

This clinical management of Sickle Cell Disease (SCD) guidelines were developed by a standard of Care Working group composed of healthcare personnel with expertise in paediatric and adult haematology and clinical psychology. This initiative was started after the establishment of a “Sickle Cell Disease in Sub-Saharan Africa: Collaborative Consortium after being awarded the National Heart, Lung and Blood Institute (NHLBI) of the National Institute of Health (NIH) of the United States of America grant(1U24HL135881-01). This grant was awarded to a multinational collaboration among Muhimbili University of Health and Allied Sciences (MUHAS), Dar es Salaam, Tanzania as hub and three sites; MUHAS, Dar es Salaam, Tanzania, University of Abuja, Abuja, Nigeria and The Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.

Its first goal was to reduce morbidity and mortality in SCD in Africa through implementation research demonstrating the feasibility of introducing newborn screening (NBS) and providing comprehensive care to prevent, identify, treat, and manage acute and chronic complications. Specific aim 2 of the proposal was to develop, implement and evaluate a resource-based, multi-level, “Guidelines for Management of SCD in SSA”.

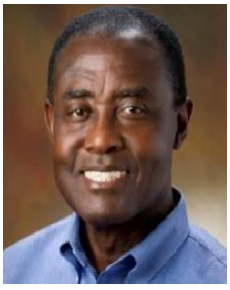
This work was done under the esteemed leadership of Prof Kwaku Ohene Frempong (KOF), (Sickle Cell Foundation of Ghana) who demonstrated exceptional dedication and unwavering commitment to improving the lives of SCD patients. The innovative design approach developed by the KOF and the Foundation using a multi-referral level guideline approach formed the blueprint for the creation of these guidelines, empowering healthcare professionals across the region to provide evidence-based and compassionate care to those in need. Both African and non-African SCD guidelines were used to draft locally appropriate SCD management recommendations.

The purpose of these guidelines is to guide healthcare professionals at the last referral level to be able to help people living with sickle cell disease (SCD) so that they receive appropriate care. The target audience are clinicians, nurses, and staff who provide emergency or continuity care to individuals with SCD at the last referral hospitals.

The guidelines focus on recommendations for Diagnosis of Sickle Cell Disease (SCD) and Related Conditions, Health Maintenance and Preventive Therapy, screening for Specific Complications of Sickle Cell Disease, Management of Acute Complications of SCD, Management of Chronic Complications of Sickle Cell Disease and Special Management Protocols including hydroxyurea protocol, blood transfusion among a few. The recommendations address the care of infants, children, adolescents, and adults with SCD, with the goal of facilitating high-quality and appropriate care for all individuals with this disease no matter where they find themselves.

As we embrace these guidelines within the SPARCo consortium, we acknowledge the immense responsibility bestowed upon us to carry forward the legacy of Professor Kwaku Ohene Frempong.

Together, we embark on this transformative journey, equipped with the wisdom of the past and the hope of the future, guided by the vision of Professor Kwaku Ohene Frempong, and committed to making a lasting impact on the lives of SCD patients in Sub-Saharan Africa.



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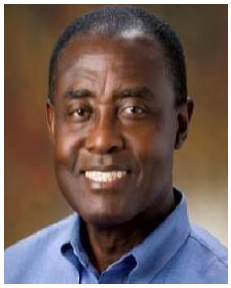
LIST OF CONTRIBUTORS



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ACKNOWLEDGEMENT

We sincerely thank everyone who contributed significantly to the development and improvement of the guidelines. Their invaluable suggestions and insights have significantly raised the caliber and efficacy of guidelines.

For internal reviewers, despite their demanding schedules and numerous responsibilities, they generously devoted their time and effort to thoroughly review the guidelines. Their meticulous attention to detail and comprehensive feedback significantly contributed to the overall improvement of the document. We are truly indebted to their expertise and commitment to patient care.

Furthermore, we would like to express our heartfelt appreciation to our external reviewers, who willingly took time out of their busy schedules to evaluate our rules. Their external perspective and diverse variety of experiences boosted our work and offered us useful ideas from various healthcare settings. Their constructive criticisms and ideas unquestionably improved the quality and applicability of our guidelines.

In addition, we would like to express our appreciation to the principal investigators (Prof Julie Makani and Prof. Ambroise Wonkam) for their unwavering support throughout the development process. Their guidance, expertise, and encouragement were instrumental in steering the project in the right direction. Their commitment to evidence-based medicine and patient-centered care has been a driving force behind the success of this endeavor.

We also want to thank the administrative and technical staff at the SPARCO Hub in Tanzania and SADaCC, in Cape Town who were instrumental in ensuring the smooth functioning of the entire process. Their technical expertise and tireless efforts in managing data, coordinating meetings, and overseeing the logistics of the process were invaluable. Without their dedication and proficiency, these guidelines would not have been executed with such precision and efficiency.

Last but not least, we thank the National Institutes of Health for funding this project. Their generous support and belief in our vision have been instrumental in bringing this project to fruition. Their financial support enabled us to do significant research, engage professional reviewers, and promote the guidelines to a large audience. We are deeply appreciative of their commitment to improving disease management and healthcare outcomes.

Finally, we want to underline that the successful completion of these management standards was a joint endeavor that required the dedication, knowledge, and assistance of numerous individuals. Each and every contributor, whether internal or external, played an integral role in shaping the final outcome. Their commitment to quality and patient care has made a lasting impact on the healthcare community. Thank you once again for your invaluable contributions and unwavering support.

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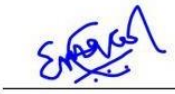

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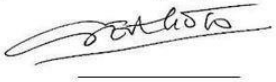

Prof.Alex Osei-Akoto **(PI)**, **GHANA site**

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LIST OF ACRONYMS

ACN	Acute Chest Syndrome
ASS	Acute Splenic Sequestration
AVN	Avascular Necrosis
CE	Capillary Electrophoresis
CAE	Cellulose Acetate Electrophoresis
CAGE	Citrate Agar Gel Electrophoresis
CBT	Cognitive Behavioral Therapy
CT	Computerized Tomography
CTT	Chronic Transfusion Therapy
ECG	Electrocardiography
ERCP	Endoscopic Retrograde Cholangiopancreatography
FBC	Full Blood Count
Hb	Haemoglobin
HE	Haemoglobin electrophoresis
HLA	Human Leukocyte Antigen
HLPC	High Performance Liquid Chromatography
HSCT	Haematopoietic Stem Cell Transplantation
IEF	Isoelectric Focusing
IPD	Invasive Pneumococcal Disease
LFT	Liver Function Test
MD	Maximum Dose
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MSOF	Multisystem organ failure
MTD	Maximal Tolerated Dose
MUAC	Mid-Upper arm circumference
NHLBI	National Heart, Lung and Blood Institute
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NT-proBNP	N-terminal pro-Brain Natriuretic Peptide
POC	Point-of-Care
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cells
RHC	Right Heart Catheterization
SaO2	Oxygen Saturation
SCD	Sickle Cell Disease
TCD	Transcranial Doppler
TD	Therapeutic Dose
TIA	Transient Ischemic Attack

TRCA	Transient Red Cell Aplasia
TRV	Tricuspid Regurgitant Jet Velocity
VOC	VasoocclusiveCrisis
VTE	Venous Thromboembolism
WHO	World Health Organization
6MWD	6 Minute Walk Distance

INTRODUCTION

Sickle cell disease (SCD) is the commonest clinically significant haemoglobinopathy. It was first reported in literature in November 1910 by James Herrick when he saw “peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anaemia”.(1)The sickling of RBCs contributes to vaso-occlusion and intravascular hemolysis which leads to the symptomatology these patients present with.(2)They are at increased risk of coming with several complications which can lead to mortality if the appropriate management schedule is not instituted. The absence of a structured clinical management guideline can lead to lots of morbidity and mortality for the patient with SCD.

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Its first goal was to reduce morbidity and mortality in SCD in Africa through implementation research that will demonstrate the feasibility of introducing newborn screening (NBS) and providing comprehensive care to prevent, identify, treat and manage acute and chronic complications. Specific aim 2 of the proposal was to develop, implement and evaluate a resource-based, multi-level,” Guidelines for Management of SCD in SSA”. The specific objectives included reviewing existing guidelines and setting minimum standards for management of SCD based on available institutional and human resources.

The purpose of these guidelines is to guide healthcare professionals at the last referral level to be able to help people living with sickle cell disease (SCD) so that they receive appropriate care. The target audience are clinicians, nurses, and staff who provide emergency or continuity care to individuals with SCD at the last referral hospitals.

The guidelines focus on recommendations for Diagnosis of Sickle Cell Disease (SCD) and Related Conditions, Health Maintenance and Preventive Therapy, Screening for Specific Complications of Sickle Cell Disease, Management of Acute Complications of SCD, Management of Chronic Complications of Sickle Cell Disease and Special Management Protocols including hydroxyurea protocol, blood transfusion among a few. (4) The recommendations address the care of infants, children, adolescents, and adults with SCD, with the goal of facilitating high-quality and appropriate care for all individuals with this disease no matter where they find themselves.

CHAPTER 1

DIAGNOSIS OF SICKLE CELL DISEASE (SCD) AND RELATED CONDITIONS.

In the diagnosis of sickle cell disease (SCD), tests for hemoglobin (Hb) type using Hb separation or specific immunologic methods, and DNA-based mutation analyses for confirmation can be done, if necessary.

Use a hemoglobin (Hb) separation method for initial determination of Hb phenotype. These include: Hb electrophoresis (HE) - cellulose acetate (CAE) at alkali pH; citrate agar gel electrophoresis (CAGE) at acid pH - etc.; isoelectric focusing (IEF); capillary electrophoresis (CE); and, high performance liquid chromatography (HLPC). Confirm results showing Hb variants using a method different from the original test as the Hb separation methods are seldom definitive. (5)(6) For children less than 6 months of age: do not use CAE at alkali pH; use IEF, CE, HPLC, or CAGE at acid pH for such young children. Contact National Newborn Screening Programme for referral to laboratory with appropriate methodology for newborns.(6)

Tests to diagnose heterozygous beta thalassemia (trait) in those with "No Hb variant" visible by the Hb separation methods (Hb phenotypes FA, AF, AFA2, AA2F, AA2, A).

In order to help determine the presence of beta or alpha thalassemia, obtain full blood count (FBC) using electronic analyzer to look for elevated RBC count with microcytic hypochromic indices. Rule out iron deficiency as cause of microcytic hypochromic indices. Determine relative amounts (%) of Hb fractions (Hb A2, F, A/S ratio, etc.) - using densitometry, chromatography, etc., especially in testing for genetic counseling purposes. If such testing is not available, refer the person to a laboratory with such capability.

Rapid Screening and Point of Care tests for Hb S, C, A

Use solubility or slide sickling test for rapid screening for presence of Hb S in a clinically ill person in order to guide treatment decisions. Do not use solubility or slide sickling test in children less than 6 months of age. You may use these "functional" tests to confirm the identity of Hb fraction suspected of being Hb S. You may use solubility or slide sickling test in emergency to rule in the presence of Hb S, and the possibility of SCD, in order to guide clinical decision. Use other point-of-care (POC) tests for rapid screening for presence of Hb A, S, and C, or other hemoglobin's, depending on the validated diagnostic ability of the specific POC test. You may use POC test in emergency to rule out SCD in an undiagnosed person in order to guide clinical decision, or in a person seeking SCD-related Hb identification for genetic counseling purposes.

Do not use solubility, sickling, or POC tests alone to diagnose SCD, sickle cell trait, or establish Hb phenotype. Use other methods to help confirm results and true Hb phenotype or genotype. (6)

DNA- based tests

Send samples to laboratories with DNA analysis capability to confirm Beta-S and other related mutations, such as deletional HPFH genotypes, especially when parental Hb analyses are unavailable.

CHAPTER 2

HEALTH MAINTENANCE AND PREVENTIVE THERAPY

Infection Prevention: General

Teach and continually remind families of children or older people with SCD to seek immediate medical attention for fever (temperature greater than 38.3°C and other signs of infection). Teach families of children with SCD and adults with SCD to own and learn how to use a thermometer. (Use axillary temperature in infants and young children). Teach about basic hygiene and preventive measures such as hand washing with soap and use of sanitary gels, especially after use of toilet and changing of infants and toddlers, and before eating. (7)(8)

Prevention of invasive pneumococcal disease (IPD)

Administer oral penicillin prophylaxis (125 mg for age <3 years and 250 mg for age ≥3 years) twice daily until age 5 in all children with HbSS. (9) (10) (11) Patients with a penicillin allergy may be placed on the equivalent dose of oral erythromycin. Clarithromycin can also be used in Penicillin allergic patients. Discontinue prophylactic penicillin in children with SCD-SS at age 5 unless they have had a splenectomy or invasive pneumococcal infection. (NIH) When discontinuing penicillin prophylaxis at age 5, it is important to assure that the child has completed the recommended pneumococcal vaccination series, and if not, complete the series immediately. Children with SCD who have had previous invasive pneumococcal disease such as pneumonia, septicemia, or meningitis, those whose immunizations are not up-to-date, and those who have had a surgical splenectomy should continue on penicillin prophylaxis indefinitely. Indefinite prophylaxis should also be considered for children with inconsistent compliance with antimicrobial prophylaxis. Assure that people of all ages with SCD have been vaccinated against Streptococcus pneumonia. Remind people with SCD, their families, and caregivers to seek immediate medical attention whenever fever (temperature greater than 101.3°F or 38.5°C) occurs, due to the risk for severe bacterial infections. (5)

Prevention of malaria

In countries with low transmission, no Prophylaxis prescribed. Use insecticide treated nets and indoor residual spraying to help reduce malaria infections. Prompt diagnosis and treatment according to the country's guidelines. Recommend that if malaria prophylaxis is in the country's guidelines, give the recommended drugs. (11)(5)

Prevention of enteric gram-negative organisms (salmonella, E. coli, Klebsiella, etc.)

Teach about basic hygiene and preventive measures such as hand washing with soap and use of sanitary gels, especially after use of toilet and changing of infants and toddlers, and before eating. No vaccines or chemoprophylaxis recommended.

Immunization

All individuals with SCD should receive all immunizations according to the country specific schedule. Because of their increased susceptibility to invasive pneumococcal disease, all infants with SCD should receive the complete series of the 13-valent conjugate pneumococcal vaccine series beginning shortly after birth and the 23-valent pneumococcal polysaccharide vaccine at age 2 years, with a second dose at age 5 years. Immunization of Special Interest to SCD: Vaccinate ALL people with SCD against pneumococcus, Hemophilus influenzae type b (Hib), Hepatitis B and meningococcus, according to schedule approved for the country. Salmonella typhi immunization can be given to those at risk of Salmonella infection. (12)

Nutrition

At each medical visit, a nutrition-focused physical examination should be performed to screen for the presence of nutrient deficiencies. Also, a mandatory weight measurement is recommended for monitoring and institution of appropriate nutritional interventions. Encourage exclusive breast feeding for the first 6 months of life. Complementary feeding should be introduced from 6 months with proteins (liver, meat, fish and beans), fruits, potatoes, yam and green leafy vegetables. (5) Thereafter, they should be encouraged to have a balanced diet. Choose a diet with a wide variety of foods from all food groups each day. Each day include items from: Starches (e.g., yam, potato, rice, maize); Protein (e.g., red meat, fish, chicken); Fruits (e.g., mango, oranges, banana, tomato); Vegetables (e.g., cabbage, carrot, spinach); Diary products (e.g., milk, cheese); and, Fats (e.g., margarine, butter). During painful episodes, the appetite will be poor. If this occurs, give protein-energy supplements. Encourage all patients with SCD to drink plenty of fluids regularly, at least 3-4 liters/day in adults, in order to reduce the risk of dehydration, raised by hyposthenia and nocturnal enuresis. Early referral to a Registered Dietitian is essential for nutrition screening and assessment, which should include an ascertainment of malnutrition risk, an assessment for possible weight loss and nutrient deficiencies, and education and planning for the management of nutritional concerns.

Growth and Development monitoring in children

Serial growth measurements should be performed to capture both acute changes and long-term growth velocity. 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 should be >12.5cm from 1-5years. Recumbent length for infants should be measured supine until 24 months of age; head circumference should be measured serially until an infant reach at least 36 months of age. Age-appropriate growth charts should be used to identify suitable trajectories in growth in infants, children, and adolescents, and identify suboptimal growth. (5) Parents/Caregivers should be educated that the children may have reduced weight and height when compared with their peers, but that may catch up in growth especially during adolescence. (5)

Genetic and reproductive counseling

Counseling should be done by trained personnel. Adhere to the counseling procedures. Be friendly, empathic and ensure confidentiality. Ensure maximum comfort and minimum distractions. Provide accurate information about the disease. Use local language to facilitate understanding. Encourage patients with SCD to have a reproductive plan. This includes knowing the haemoglobinopathy status of the partner.

Female reproductive health (Pregnancy, Contraception and Fertility)

Contraception - Educate on the use of contraception. No contraindications for any of the usual contraceptives. Preconception - Stop Hydroxyurea 3 months before conception. Iron chelation should be stopped during pregnancy. Discuss with patient about the risks associated with pregnancy in SCD, both maternal and fetal risks. Also determine the haemoglobinopathy status of the partner. Document pre-pregnancy baseline results (CBC, Blood grouping and Antibody screening, Renal and Liver function tests, serum ferritin levels, baseline Hb S%, serology for HIV, HBV, HCV). Pregnancy - Refer to a high-risk antenatal clinic for follow up. Take thorough history and physical examination. The history should include past obstetric and medical complications. Prescribe routine prenatal vitamins. Give 75mg of aspirin after 12weeks to reduce risk of pre-eclampsia. Prophylactic blood transfusion is not recommended. Delivery - Plan mode of delivery. Vaginal delivery is preferred, unless there is indication for caesarian section. Monitor maternal hydration, warmth and adequate analgesia. Postpartum - Consider use of venous thromboembolism prophylaxis for patients with additional risk factors for VTE e.g., previous history of VTE, caesarian section or immobility. (7)(8) Counsel about use of contraception. Assess and manage neonatal opioid dependency and withdrawal all infants with history of in utero opioid exposure.

Male reproductive health

Encourage men with SCD to have reproductive life plan and to decide whether to have children or not and the implications. Counsel and educate men with SCD about heritability of SCD. Provide pre-marital counseling to a man with SCD together with his fiancée with a view of the fiancée undergoing a haemoglobinopathy screening.

Education and psychosocial counseling

Educate all children from school going age with their parents/caregivers and adults routinely about SCD at each visit: utilize available materials e.g., brochures, videos, and apps. Talk to patients and parents, encourage them to talk about daily problems including finance and poverty, offer practical solutions. Prompt patients and parents to talk about stigma and their experience with how their communities and others relate to them, dispel myths. Educate parents/caregivers about importance of schooling, encourage their children to attend school when they are well and to keep a record of the number of school days lost. Encourage adults to find employment (paid or voluntary).

Encourage patients to participate in social activities and not feel isolated. Encourage participation in support groups where available. Encourage self-management and reinforce health maintenance. Ensure understanding of the importance of adherence to medical advice and treatment. Offer psychoeducational sessions: individual and/or group or family sessions as appropriate

Organizing support groups.

Suggest to patients and parents about setting up a support group if one is not available for them, they should also consider social media support groups. Encourage patients and parents to organize their own groups but consider what healthcare or other professional support is required. Help identify organizers/leaders for the group but emphasize that everyone has a role to play and can take turns, and be open to suggestions and contributions. Consider how the group is structured e.g., parents of newborns and infants, teenagers only, group size and scope of support. Consider the time and place to meet, frequency, length, cost of venue (free or cheap) e.g., school, church, library or other public venue suitable and accessible for everyone, and available transportation. Consider how patients or parents will be encouraged to join e.g., clinic flyers, personal invitations, social media. Consider some ground rules and how to solve problems e.g., confidentiality, a person talking too much, someone who is upsetting others within the group, someone not well enough to attend and has responsibilities. Consider fundraising and/or contribution from members towards sustainable running costs, refreshments, and social activities. Consider whether to formalize the group after a while to become a registered charitable organization.

Transition of adolescents to adult care.

Start preparation and plan the transfer at an early age in a developmentally appropriate manner. There should be a collaboration between pediatric and adult SCD health care providers to facilitate an effective transition. Carry out a detailed review at various time points to evaluate knowledge and understanding about SCD, and readiness for transition.

The pediatric health care providers should send a complete summary to the adult SCD health care providers. The summary should include details about SCD-related complications, investigations and treatment.

Travel management

Patients should be encouraged to seek travel advice and to accept all the offered immunizations relevant to the area to which they are travelling; this includes live vaccines like yellow fever. Patients with SCD should receive malaria prophylaxis when travelling to malarial areas from a non-endemic country in line with general guidance for the area of travel. (13)

CHAPTER 3

SCREENING FOR SPECIFIC COMPLICATIONS OF SICKLE CELL DISEASE

Screening for Stroke Risk.

Transcranial Doppler ultrasonography (TCD).

Obtain transcranial Doppler ultrasonography (TCD) at least once annually in children 216 years old, with severe SCD (SCD-SS or SCD-S^{o} only). Arrange for the child to visit a center where TCD can be performed, or, arrange for portable TCD screening to be performed for children at your facility on a periodic basis, If TCD is not available at your facility. Start chronic transfusion therapy (CTT) or, refer the child to a center where CTT can be started, with the goal of maintaining pre-transfusion Hb S < 30% in order to prevent occurrence of stroke, if TCD blood flow velocity is "abnormal" ($\geq$ 200 cm/sec). (7) Give hydroxyurea, following a recommended protocol, where chronic transfusion therapy is not possible. (8) Use a maximal tolerated dose (MTD) / maximum dose (MD) protocol to adjust hydroxyurea dose to the Therapeutic Dose (TD) at which Hb 10 g/dL is achieved and maintained. (See Guidelines for Hydroxyurea Therapy). Repeat TCD every 3-4 months in those treated with hydroxyurea, or with Conditional blood flow velocity (170199 cm/sec); and, every 12 months for those on CTT, or those with Normal blood flow velocity (<170 cm/sec). (8) (14)

Magnetic resonance imaging (MRI) and angiography (MRA)

Perform routine screening with brain magnetic resonance imaging (MRI) and angiography (MRA) to detect and monitor silent cerebral infarcts (SCI), if available on site, or refer to another facility where it is available. Follow recommendations for transfusion similar to those for abnormal TCD above, if MRI is positive for SCI. Give hydroxyurea, following a recommended protocol, where chronic transfusion therapy is not possible. Use a protocol for hydroxyurea therapy similar to that recommended for children with abnormal TCD. (8) (14) (15)

Screening for Renal Disease

Screen all individuals with SCD, beginning by age 10, for proteinuria. If the result is negative, repeat screening annually. If the result is positive, perform a first morning void urine albumin-creatinine ratio and if abnormal, consult with or refer to a renal specialist. Patients with hematuria should be referred to a secondary or tertiary health facility for exclusion of other causes. Encourage high fluid intake. (7) (14)

Screening for Retinopathy

Refer a person with SCD to an ophthalmologist for a dilated eye examination to evaluate for retinopathy beginning at age 10 years. Re-screen for retinopathy at 1–2-year intervals, if the results remain normal. Refer people with suspected retinopathy to a retinal specialist ophthalmologist for management. (14)

Screening for Pulmonary Disease.

In children and adults with SCD, assess for signs and symptoms of respiratory problems (such as asthma, COPD, restrictive lung disease, or obstructive sleep apnea) by history and physical examination. In children and adults with SCD found to have signs or symptoms of respiratory problems, further assessment including pulmonary function tests is recommended to determine the cause and develop a plan to address it. Do not screen asymptomatic children and adults with pulmonary function tests.

Screening for Cardiovascular Disease.

All adults (age >18yr) with severe SCD (SCD-SS, SCD-Sβ^O, SCD-OArab) should have a baseline echocardiogram, and every 3 to 5 years, if results remain normal. Children, with symptoms suggestive of heart disease should be evaluated for cardiac disease, including echocardiography. Routine echocardiography is not necessary in children (age <18 yr.) with no symptoms suggestive of cardiac disease. New symptoms and signs of cardiac dysfunction should be investigated with echocardiogram and evaluated by a cardiologist.

Electrocardiography screening for cardiac disease.

Routine ECG screening is not recommended in patients with SCA. Perform ECG to exclude myocardial infarction in patients with SCA presenting with acute chest pain.

Screening for pulmonary hypertension.

Evaluation: 1. All adults (age >18yr) with severe SCD (SCD-SS, SCD-Sβ^O, SCD-OArab) should have a baseline echocardiogram, and every 3 to 5 years, if results remain normal. Children, with symptoms suggestive of heart disease should be evaluated for cardiac disease, including echocardiography. Routine echocardiography is not necessary in children (age <18 yr.) with no symptoms suggestive of cardiac disease. 2. New symptoms and signs of cardiac dysfunction should be investigated with echocardiogram and evaluated by a cardiologist. Measure N-terminal pro-brain natriuretic peptide (NTproBNP) and/or 6-minute walk distance (6MWD). 3. If pulmonary arterial pressure (PAP) is >40mmHg or tricuspid regurgitation jet velocity (TRV) is >2.5m/sec or NT- proBNP is > 164.5pg/mL and/or low 6MWD is ≤333m do confirmatory test (right heart catheterization). 4. Exclude other associated conditions such as thromboembolic disease,

iron overload, systemic hypertension, obstructive sleep apnea, and chronic hypoxemia must be ruled out and treated. Management: Persons with pulmonary hypertension should be comanaged by cardiologist or pulmonologist and hematologist or SCD doctors

Screening for Hypertension

In children with SCD, measure blood pressure at every routine visit, and evaluate and treat hypertension following established local standards or recommendations from the NHLBI's "Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents." In adults with SCD, screen for hypertension at every visit and treat to lower systolic blood pressure ≤140 and diastolic blood pressure ≤90 according to established local standards or recommendation in "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC 7). For patients with albuminuria (albumin creatinine ratio [ACR] ≥3.5mg/mmol) target blood pressure should be 130/80. If BP is ≥ 130/80 in the presence of proteinuria initial treatment should be with an ACE inhibitor or angiotensin receptor blocker (ARB) or a calcium channel blocker. In the absence of proteinuria initial treatment should be with calcium channel blockers

Screening for red cell antibodies related to pregnancy

Perform antibody screening and identification in pregnant women during the first antenatal clinic visit. Screen partner for presence of antigens corresponding to the antibodies found in the expecting mother. This will determine the risk of fetus to develop hemolytic anemia. Store the antigen matched blood if complications are anticipated in a pregnant woman with multiple alloantibodies.

CHAPTER 4

MANAGEMENT OF ACUTE COMPLICATIONS OF SCD.

Acute Anemia

Defined as the rapid significant fall in Hb of at least 2g/dl from baseline levels. It is usually caused by transient red cell aplasia (TRCA), acute splenic sequestration (ASS) and accelerated hemolysis due to sepsis, delayed hemolytic transfusion reaction, and hyper hemolytic syndrome. (14) (16) Assess for the cause of acute anemia (TCRA, ASS, infection, or delayed transfusion reaction.). Do CBC and reticulocyte count, repeat at least daily and compare the results. In ASS, first give intravenous fluids carefully to prevent hypovolemic shock; monitor vital signs carefully. Type and cross match RBC and transfuse carefully in small aliquots – starting with number of ml/kg of red cells equal to Hb number/dL. E.g., for patient with Hb 3/dL, give 3 ml/kg of packed RBC as initial transfusion; wait 3-4 hours for equilibration and give subsequent small volume transfusions as needed. Do not aim for baseline or normal Hb level in initial transfusions or Hb level > 10g/dL, if baseline Hb is not known, in order to reduce the risk of hyper viscosity and stroke. (7) (15) Do blood and urine culture if sepsis is suspected. Do chest X-ray if signs of respiratory pathology are present. Do serum IgM for Parvovirus B19 or presence of Parvovirus DNA to confirm the diagnosis of aplastic crisis. Treat the cause of acute anemia accordingly. Isolate patients with aplastic crisis. Particularly from expectant mothers, as infection may result in hydrops fetalis, fetal death or congenital anemia. Investigate other relatives with SCD who are exposed to patients with aplastic crisis. (16)

Acute Chest Syndrome

Evaluate people with SCD who develop acute onset of signs and symptoms of lower respiratory tract disease with or without fever for ACS. Obtain a chest x-ray and measure oxygen saturation by pulse oximetry. Admit patients with SCD and ACS. Treat people with SCD who have ACS with an intravenous cephalosporin, an oral macrolide antibiotic, supplemental oxygen (to maintain oxygen saturation of greater than 95 percent), and close monitoring for bronchospasm, acute, and hypoxemia. Give simple blood transfusion (10 mL/kg red blood cells) to improve oxygen carrying capacity to people with symptomatic ACS whose Hb level is >1.0 g/dL below baseline. If baseline is 9 g/dL or higher, simple blood transfusion may not be required. Perform urgent exchange transfusion—with consultation from hematology, critical care, and/or apheresis specialists—when, in spite of simple transfusion, there is rapid progression of ACS with oxygen saturation below 90 % despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, and/or decline in Hb level. Encourage

ambulation, activity, deep breathing exercises and tools such as, incentive spirometer, balloon blowing, or equivalent methods.

Acute SCD pain (Vaso occlusive pain episode, VOPE, or "pain crisis").

In adults and children with SCD and pain, when indicated, initiate diagnostic evaluation of causes of pain other than a VOC while beginning to treat pain. In adults and children with SCD and a VOC, determine characteristics, associated symptoms, location, and intensity of pain based on patient self-report and observation. Use pain assessment toolto assess the degree of pain. (17) If the VOC pain is atypical, investigate other possible etiologies of pain. Rapidly assess the patient's recent analgesic use (opioid and no opioid). Rapidly initiate analgesic therapy within 30 minutes of triage or within 60 minutesof registration. (7)(8) Base analgesic selection on pain assessment, associated symptoms, outpatient analgesic use, patient knowledge of effective agents and doses, and past experience with side effects. Use the WHO 3 strategies for managing pain in adults or 2 step strategy for children. In children with SCD and a VOC associated with mild to moderate pain who report relief with NSAIDS, in the absence of contradictions tothe use of NSAIDS, continue treatment with NSAIDS. In adults and children with SCD and a VOC associated with severe pain, rapidly initiate treatment with parenteral opioids.
(16) (18) Reassess and re-administer opioids if necessary for continued severe pain every 15 -30minutes until pain is under control per patient report and also assess for side effects. (8) (18) In adults and children with a VOC, administer oral NSAIDS as an adjuvant analgesic in the absence of contraindications. To reduce the risk of acute chest syndrome in adults and children hospitalized for a VOC, encourage use of incentive spirometry while awake and encourage ambulation and activity as soon as possible. Give supplemental oxygen if hypoxemic. (8) (16) In adults and children with VOC, use adjunctive non-pharmacologic approaches to treat pain such as local heat application and distraction. In euvolemic adults and children with SCD and a VOC who are unable to drink fluids, provide intravenous hydration at no more than maintenance rate to avoid over hydration. In adults and children with SCD and a VOC, do not administer a blood transfusion unless there are other indications for transfusion. Discharge patient when pain is improving or controlled with reduced dose of oral analgesia and arrange for outpatient follow up appointment as applicable. (5)

Acute Splenic Sequestration

Do complete blood count, reticulocyte count, blood grouping and cross match. Give IV fluid to correct hypovolemia as per hydration guideline. Type and cross match RBC and transfuse carefully in small aliquots – starting with number of ml/kg of red cells equal to Humberto grams/dL. E.g., for patient with Hb 3g/dL, give 3 ml/kg of packed RBC as initial transfusion; wait 3-4 hours for equilibration and give subsequent small volume transfusions as needed. Do not aim for baseline or normal Hb level in initial transfusions

or Hb level > 10g/dL, if baseline Hb is not known, in order to reduce the risk of hyper viscosity and stroke. (7)(8)(5) The sequestered red cells can reenter circulation hours or days after RBC transfusion and may increase the risk of hypovolemic shock, acute cardiac failure, hypertension and stroke. Monitor spleen size for recurrence.

Do splenectomy for patients with recurrent sequestration or a single life-threatening acute sequestration episode. Give penicillin prophylaxis post splenectomy. (17)

Acute Stroke

Promptly and carefully examine for acute stroke or transient ischemic attack (TIA) a child or adult with SCD who presents with active or recent history of hemi- or monopoiesis, altered level of consciousness, seizures, speech problems, or severe headache. (7) (17) Seek neurologist consultation, if available. Stabilize vital signs. Obtain urgent brain computerized tomography (CT) scan, if available, to rule out hemorrhage that may require neurosurgical intervention. In consultation with a sickle cell expert, perform exchange transfusion with a goal to reduce Hb S to < 30%, in people with SCD who develop acute stroke confirmed by neurologic examination or neuroimaging. If exchange transfusion is not available perform a simple transfusion. (8) (19) (See Guidelines for Blood Transfusion in SCD).

Fever and other signs of infection

Patients with SCD are at risk of overwhelming septicemia with encapsulated organisms due to loss of splenic function. (14)

Investigations to be requested will include the following; Full blood count, blood cultures, and malaria test, Urinalysis (dipstick), urine microscopy, and urine culture/sensitivity, Group and cross match, Creatinine, urea, electrolytes, Chest x-ray if any respiratory symptoms/signs, Bone imaging +/- orthopedic review +/- joint aspiration if any limb symptoms,

If signs of meningeal irritation or child <18 months with unexplained fever, consider lumbar puncture

Insert IV cannula. **IV FLUIDS** – Hydrate, as per hydration guideline**.** Start appropriate antibiotics, broad spectrum, as per local guideline for specific infection or septicemia. Consider: malaria treatment, oxygen, pain relief, transfusion if indicated. HOURLY OBSERVATIONS for first 6-12 hours – pulse, respiratory rate, SaO2, temperature, Glasgow Coma Score. Be alert for complications e.g. Acute chest syndrome, stroke. (8) (15) (20)

Osteomyelitis and septic arthritis

Investigations: Blood culture, direct bone aspirate or joint aspirate, Ultrasound, X-Ray, MRI/PET. Start with an initial broad-spectrum intravenous antibiotic awaiting the culture results for between 5-7days. Continue with oral antibiotics for the recommended minimum of 6 weeks. In absence of cultures, use antibiotics with good Salmonella and *Staphylococcus aureus* coverage. (15) Obtain urgent orthopedic consultation.

Multisystem Organ Failure

Evaluate for potential Multisystem organ failure (MSOF) all patients with VOC exhibiting severe deterioration. Support with supplemental oxygen and mechanical ventilation when indicated in patients with respiratory failure. Manage acute renal failure with renal replacement therapy e.g., Dialysis. Immediately consult hematologist or SCD expert and initiate simple or exchange transfusion (see SCD Transfusion guideline). (8)

Priapism

Acute fulminant (Major) Priapism

Document the time of onset, and precipitating factor, if any. Management includes education of males with SCD in childhood about priapism and encourage them to inform their parents/guardians or doctors if it occurs.

Emphasize that it is a medical emergency for episodes less than 2 hours in onset. Encourage patient to micturate, have a warm bath or walk around; Also ensure adequate hydration with oral or intravenous fluids. Give adequate analgesics and anxiolytics.

For episodes lasting more than 2 hours: Consult or refer to Urologists meanwhile, Continue hydration, analgesics and sedation. Keep patient nil per oral in case of surgical intervention. Group and cross match for possible exchange transfusion.

Urologist should also aspirate and irrigate the copora caverosa with 6-10mg of injectable etilefrine diluted in 20mls of saline. If after 1 hour there is no detumescence, perform surgical shunting. (8) (15)(5)

Acute Hepatobiliary Complications

1. Acute hepatic sequestration

Obtain FBC and LFT, and rule out other causes of rapid fall in Hb. Treat as severe acute anemia; perform simple or exchange blood transfusion, as needed (8) (15)

2. Hepatic crisis

Obtain FBC, LFT, PT/PTT, and abdominal US/MRI. Treat symptomatically; monitor closely for potential deterioration (14) (15)

3. Intrahepatic Cholestasis

Obtain FBC, LFT, Abdominal US/MRI. Admit and monitor closely. Perform exchange blood transfusion (8) (15)

4. Choledocholithiasis

Obtain FBC, LFT, Abdominal US/MRI, Endoscopic retrograde cholangiopancreatography (ERCP). Consult the surgeons (14) (19)

Acute Ocular Complications

Immediately examine for hyphemia anyone with SCD who presents with eye trauma. If hyphemia is present, immediately refer to an ophthalmologist for further management. Promptly refer anyone with SCD exhibiting signs and symptoms such as protrusion of the eye, changes in visual acuity (flashers or floaters), and unilateral or bilateral loss of vision to an ophthalmologist capable of performing a dilated eye exam to assess visual acuity, intraocular pressure, and the peripheral retina. Manage acute ocular complications in consultation with an ophthalmologist, hematologist, and other specialists with expertise in SCD. (7)(8) (14) (15)

Acute Renal Failure

In the setting of an acute rise in serum creatinine of ≥ 0.3 mg/dL, (265 µmol/L) - Monitor renal function daily, including serum creatinine and fluid intake/output. Avoid potential nephrotoxic drugs and imaging agents. Evaluate the person thoroughly for all potential etiologies in consultation with a nephrologist as needed. Do not give blood transfusions to treat ARF unless there are other indications for transfusion. Use renal replacement therapy (e.g., hemodialysis) when needed for acute renal failure. (8) (19)

CHAPTER 5

MANAGEMENT OF CHRONIC COMPLICATIONS OF SICKLE CELL DISEASE

Avascular necrosis

a. Evaluation: Obtain x-ray of the joint and, obtain MRI early in the course. b. Management: I. Counsel patient to minimize movement and bearing heavy weight on affected joint. ii. Administer analgesics (non-steroidal anti-inflammatory agents ±/or opiates. iii. Refer for Orthopedic assessment, treatment, and for surgical management. iv. Give disease modifying therapy such as hydroxyurea to prevent progression or involvement of other joints (14)(5)(7)

Cardiac complications

Assess all patients for cardiac symptoms (dyspnea, dizziness, chest pain, ankle swelling) and perform cardiac examination that includes assessment for signs of right heart strain at each annual review. Patients with cardiorespiratory symptoms and signs should be evaluated with electrocardiography (ECG) and echocardiography. In patients with sickle cell disease echocardiography should be performed at initial presentation to adult service and at least once every three to five years even in asymptomatic patients (or earlier if patients are symptomatic or hypoxic). Echocardiography should be repeated annually in patients with previously elevated tricuspid regurgitant jet velocity (TRV) who have not had right heart catheterization (RHC). Patients should be referred to a pulmonary hypertension specialist center for consideration of RHC if: - TRV >290 cm/sec; or, TRV 250-290 cm/s and symptoms suggestive of pulmonary hypertension. (19)

Chronic hypersplenism

Do Complete blood count, reticulocyte count, Peripheral blood film. Monitor spleen size and document at every clinic visit. Exclude and treat other causes of cytopenia. Do splenectomy if hypersplenism is associated with failure to thrive, critical indices (Hb<5g/dl, platelets < 50 X 10^9/l) or chronic pain. Give penicillin prophylaxis for a minimum of 3 years post splenectomy (5) (14)

Chronic Pain

SCD pain is considered chronic if it lasts more than 3 months. Determine the cause and type of SCD-related chronic pain. This includes chronic pain with objective signs such as avascular necrosis (AVN) and leg ulcers, and chronic pain without objective signs due to neuroplasticity of the peripheral or central nervous system. Use a combination of the patient's response to treatment—including pain relief, side effects, and functional outcomes to guide the long-term use of opioids. Use long- and short-acting opioids to manage chronic pain that is not relieved by nonopioids. Encourage people receiving

opioids to increase their fluid intake, maintain high dietary fiber intake and to use stool softeners and bowel stimulant laxatives such as Senna as needed. Encourage people to use deep tissue/deep pressure massage therapy, muscle relaxation therapy, and self-hypnosis. Assess all people with SCD for chronic pain annually or more often as needed.

This assessment should include descriptors of the pain, its severity on a numerical scale, its location, factors that precipitate or relieve it including biopsychosocial factors and its effects on the patient's mood, activity, employment, quality of life and vital signs. Consider management of neuropathic pain by antineuralgic, tricyclic antidepressants, e.g., amitriptyline. Patients with progressive musculoskeletal conditions should be referred to orthopedic or rheumatology specialist. Refer for evaluation by psychologist - to relieve anxiety / depression stemming from disability, job absences or financial difficulties. Refer to occupational therapist and physiotherapist to assist patients to gain optimum physical function and independence. (14)

Endocrine complications

Gonadal Dysfunction (low testosterone)

1. Gonadal Dysfunction (low testosterone)

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

If at the age of 14years in male patients there is evidence or symptoms of hypogonadism, refer to endocrinologist for evaluation and treatment (15)

2. Adrenal Dysfunction

Evaluate patients who have hemodynamic compromise during sickle cell crises with sepsis for adrenal insufficiency. Refer to an endocrinologist if there is evidence of adrenal insufficiency (15)

3. Thyroid Dysfunction

Check for a history of chronic transfusion, a recognized risk factor of hemosiderin associated thyroid dysfunction. (15)

Impaired glucose tolerance and diabetes mellitus

Perform annual glucose tolerance screening with fasting plasma glucose in chronical transfused SCD patients. Refer SCD patients with impaired glucose tolerance and diabetes mellitus to endocrinologist. (15)

Parathyroid dysfunction

Evaluation: Screening with serum calcium, phosphorus, alkaline phosphatase, parathyroid levels, and neck ultrasound to exclude hyperthyroidism. Screen for hypothyroidism in chronically transfused SCD patient from 10 years of age. Management: Refer patient with evidence of parathyroid dysfunction to the endocrinologist. (15).

Gastrointestinal complications

Acute Abdomen

Investigations: Do: I. Blood culture; ii. Serum amylase; iii. Abdominal ultrasound scan; iv. Abdominal x-ray; v. CT scan.

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

Mesenteric (Girdle) Syndrome.

Recommendations: Rule out other surgical pathologies. Manage conservatively with Intravenous fluid, analgesics and nasogastric aspiration if vomiting. Consider exchange blood transfusion (19)

Chronic Sickle Hepatopathy

Consider exchange red cell transfusion Programme. Refer to a specialist center with exercise in sickle cell hepatopathy (19)

Viral Hepatitis

Refer to hepatologist. Monitor hemoglobin concentration in patients on ribavirin because of the risk of hemolytic anemia. (19)

Iron overload

Ensure iron overload monitoring in patients receiving repeated red cell transfusion. Commence iron chelation when liver iron concentration exceeds 5-7mg Fe/g dry weight. (19)

Leg Ulcers

Assess the wound thoroughly. Document the size, appearance, status of the surrounding skin, presence of tenderness, edema and femoral lymph nodes enlargement. Do CBC and blood culture and sensitivity if associated with cellulitis or abscess formation. Do imaging studies e.g., X-rays, MRI to exclude osteomyelitis if there is fever and bone

tenderness. Apply wet-to-dry dressings twice a day. Consult the surgical team for surgical debridement and skin grafting when indicated. Give zinc supplementation. Apply graduated compression bandages to reduce lymphedema. Elevate feet when sitting to improve blood circulation to the ulcer. Treat the pain with adequate and appropriate analgesia. Usually, the pain is neuropathic in nature and it is treated with amitriptyline or newer antiepileptic drugs. (See pain management in SCD guidelines). Take biopsy for histopathology when malignancy is suspected. Consult vascular surgeons if features of arterial insufficiency present.

Consider regular blood transfusion until the wound heals if the above measures fail. Consider discontinuation of Hydroxyurea in patients with non-healing or slowly healing ulcer. Explain to the patient that ulcer may take long time to heal. Also, enforce the prevention measures to reduce the risk of recurrence. (7) (17)

Nocturnal enuresis

Routinely ask parents about nocturnal enuresis in the child with SCD aged 6 years and older. Document presence of enuresis and give information to parents and other caregivers. Assure parents that nocturnal enuresis is a known and common complication of SCD. Investigate presence of snoring, possible obstructive sleep apnea, and nocturnal hypoxemia; if these are present, refer child to ENT surgeon for further evaluation and management. Refer child to enuresis management program, if one exists, for training in use of enuresis alarms, and provide family counseling to avoid punitive measures that further lower the child's self-esteem. Try oral of nasal desmopressin if other methods fail. Do not withhold fluid intake in management of enuresis in children with SCD. (17)

Ophthalmologic Complications

Refer persons of all ages with proliferative sickle retinopathy (PSR) to an ophthalmologist (retina specialist) for evaluation and possible laser photocoagulation therapy. Refer children and adults with vitreoretinal complications of PSR refractory to medical treatment for evaluation and possible vitrectomy. (8) (17)

Psychological complications

Conduct psychological assessments for all patients (children, adults) routinely. Conduct neuropsychological assessments when neurological complications and/or educational problems are indicated. Assess mood and emotional problems. Assess physical and social function. Assess coping strategies in relation to pain, symptoms and complications. Assess general health and related quality of life. Assess attention/concentration and executive function initially, followed by comprehensive neuropsychological assessments. Offer psychological therapies e.g., cognitive behavioral therapy (CBT): individual and/or

group or family sessions as appropriate. Suggest available psychological self-help resources including internet-based interventions. Liaise with schools and colleges to negotiate additional or special educational support to compensate for neuropsychological complications and poor school performance. (17).

Pulmonary Hypertension

Evaluation: 1) Screening tests: Obtain echocardiography, measure N-terminal pro-brain natriuretic peptide (NT-proBNP), and/or 6-minute walk distance (6MWT). If pulmonary arterial pressure (PAP) is > 40mmHg or tricuspid regurgitation jet velocity (TRV) is >2.5m/sec or NT-proBNP is >164.5pg/mL and/or low 6MWT is ≤ 333m do confirmatory test. Confirmatory test: Perform right heart catheterization. Treatment: If the mean pulmonary arterial pressure (mPAP) is > 25mmHg Consult Pulmonary hypertension expert for treatment using target therapies such as: prostacyclin's analogues, phosphodiesterase type 5 inhibitors or endothelin receptor antagonists. (15) (19)

Renal Complications

If microalbuminuria or macro-albuminuria is identified, order a 24-hour urine test for protein. Refer people with proteinuria (>300 mg/24 hours) to a nephrologist for further evaluation. For adults with proteinuria without other apparent cause, initiate ACE inhibitor therapy. For children with microalbuminuria or proteinuria, consult a nephrologist. Consider patients with SCD with modest elevations of serum creatinine (>0.7 mg/dL in children, >1.0 mg/dL in adults) to have renal impairment and refer to a nephrologist for further evaluation. Give ACE inhibitor therapy for renal complications when indicated even in the presence of normal blood pressure. Renal replacement therapy (e.g. hemodialysis, peritoneal dialysis, and renal transplantation) should be used in people withSCD if needed. (14)

Seizures under neurological complications

Evaluate children and adults who present with new onset seizure for acute stroke or evidence of cerebrovascular disease. (See "Acute Stroke" above.). Evaluate children and adults who present with new seizure and no evidence of stroke for other causes of seizure such as epilepsy. Consult with neurologist to manage chronic (recurrent) seizure with appropriate anticonvulsants. Do not give meperidine (pethidine) to people with SCD who have a seizure disorder; a metabolite, normeperidine (norpethidine), a neurotoxin, is associated with seizures. (17)

Stuttering/Recurrent Priapism

Diagnosis: Take history of frequency and duration of erections and examine the phallus. Do corporal blood gas analysis and corporal doppler ultrasound?

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

Prevention. Give slow oral etilefrine starting with 25mg daily nocte. If there no satisfactory response, increase dose by 25mg every 2 weeks to a maximum of 100mg in divided doses or oral pseudoephedrine 30mg nocte in children of less than 10 and 60mg nocte in adults and children above 10 years. Consider the use of Hydroxyurea. Educate male patients and parents of adolescent patients about the risk and the emergency nature of priapism, self-treatment measures and to seek medical help if episodes exceeds 2 hours. (7) (21)

CHAPTER 6

SPECIAL MANAGEMENT PROTOCOLS

Hematopoietic stem cell transplantation

Include information about hematopoietic stem cell transplantation (HSCT) in education and counseling of people with SCD and their families; mention requirement of a matched donor, limited availability of transplant experts and centers, cost, and current outcome. Obtain human leukocyte antigen (HLA) typing, where possible, for families seriously considering HSCT as therapeutic option and include results in counseling and referrals. Arrange referrals to established centers experienced in transplants for SCD for those exploring HSCT for a person with SCD who has HLA-identical family member.

Hydration guide

Patients with SCD are at risk of dehydration due to impaired renal concentrating power and poor fluid intake. (14) Encourage oral fluids first, it should be used whenever possible. **Give IV fluids** if the patient is unable to drink well, has severe pain, abdominal symptoms, or temperature is not settling. Hydrate with normal maintenance fluid intake. Use fluids recommended for IV therapy, usually 5% Dextrose or D/S. **Stop IV fluids** when the patient is stable and, pain is controlled. Maintain a strict input/output chart for every patient. For children, weigh them daily. CAUTION. **In stroke, risk of cerebral edema, therefore, watch out for fluid overload. In acute chest syndrome, risk of pulmonaryedema, watch out for fluid overload. In these patients, initially give half of the volumes in the table. Reassess hydration status regularly and modify fluids accordingly.** (14)

Peri-operative care and surgery

Communicate with all the health care professionals involved, i.e., Surgeons, anesthesiologist, hematologist, and nursing staff. (21) Document a clear management plan before the surgery. (21) Do laboratory tests e.g., CBC, reticulocyte count, renal and liver function tests, red cell phenotyping, antibody screening and cross match preoperative. (17) (21) Transfuse phenotypically-matched red cells to raise hemoglobin level to 10g/dl, or, do exchange transfusion in patients with baseline Hb>9g/dl to reduce Hb S level to <30% before major surgery. (8) Avoid elective surgeries if patient is febrile or has an acute vasoocclusive pain. Monitor temperature, heart rates, hydration status and oxygen saturation above 95% throughout the surgery and for 24 hours after the surgery. Give prophylactic antibiotics and adequate analgesia post-operative as required. (17) Encourage early ambulation. Assess post-operative laboratory test results. Counsel

the patient and the family about the potential complications e.g., Acute chest syndrome. (17)

Transfusion Therapy in Sickle Cell Disease/Iron chelation

Consider carefully the benefits and risks of transfusion before transfusing. Obtain informed consent from parents or patient when appropriate. (17) Evaluate the patient and determine the type of transfusion required (simple transfusion vs. exchange transfusion; and, episodic vs chronic transfusion therapy.) Perform extended red cell phenotyping at first clinic visit, or just before the first RBC transfusion. Donor blood should be fully Rh and Kell compatible. (15)(8) (19) If red cell antibodies are present in patient's blood, donor red cells should be selected to avoid presence of potentially incompatible antigens. Donor RBC should be sickle negative in order to allow determination of proportion of donor RBC by determine the Hb A% and Hb S% in post-transfusion hemolysate. (15) Donor RBC should preferably be less than 7 days old. This maximizes RBC survival after transfusion and minimizes risks associated with accumulated potassium ions present in stored blood. Donor RBC should also be CMV negative when transfusing CMV negative patients. Determine target post-transfusion Hb level and calculate amount of blood product (whole blood vs. packed RBC required). Do not exceed Hb 10-11g/dL. (15)(8) In acute anemia (acute splenic sequestration, transient red cell aplasia), transfuse carefully and in small aliquots to avoid volume overload and rapid increase in blood viscosity. In chronic transfusion therapy, determine target Hb S%, e.g., < 30% Hb S in stroke prevention; measure Hb A% and Hb S% in pre-transfusion blood tests to help determine interval between transfusions and amount of RBC to transfuse in future transfusion.(8) In chronic transfusion therapy, monitor patient for iron overload (serum ferritin, hepatic iron, etc.) and plan for interventions (iron chelation therapy) to reduce or (exchange transfusion method) to prevent iron overload.(8)

Organizing SCD clinical service (outpatient routine & acute care, in patient)

There should be a network of care which include community, primary, secondary and tertiary care. Maintain clear communication between the different levels of care. Multidisciplinary team working to optimize care of patients is emphasized. Routine health checks and care for less severe complications should be provided in primary and secondary care. For major complications, care should be in specialized hospitals with appropriate facilities. Educate parents and patients about the disease during each outpatient visit. Parents' understanding of the condition is vital. Offer strategies to manage mild symptoms at home. Educate them about the symptoms that require urgent medical assessment. Monitor attendance in clinics and follow up the families who fail to attend. Take a thorough history and physical examination during consultation. Assess adherence to folic acid, penicillin prophylaxis and Hb level. Do CBC, reticulocyte count, and antibody

screening and identification during the first visit. Other investigations will depend on the clinical presentation. Review every patient at least once a year. Ask about the number of admissions, number of pain episodes and other complications.

PROTOCOL FOR HYDROXYUREA TREATMENT OF PEOPLE WITH SEVERE SICKLE CELL DISEASE

A. Patient Eligibility Criteria

1. Hb Genotype: SCD-SS, SCD-S□thal, SCD-SO $_{Arab}$ (On a case by case basis, a severely-affected person with SCD-SC may be offered HU therapy under a modified treatment protocol) (16) (10) (22)
2. Age: ≥ 12 months
3. Clinical: None
4. Social

   The adult patient, parent or legal guardian of the child patient must have demonstrated a high level of responsibility and must be regarded as capable of understanding the concepts of the therapy, follow the treatment guidelines, and be willing to comply with the required visits, laboratory evaluations, and schedule of medications. (8)(7)

B. Patient Exclusion Criteria

1. Ongoing chronic transfusion therapy
2. Chronic utilization of medications that may enhance toxicities of HU
3. Concomitant chronic illness that has the potential to increase the toxicities of HU

C. Entry Evaluation and Laboratory Studies

1. Clinical evaluation

a. Completion of History Form
b. Completion of detailed Physical Exam Form
c. Completion of Growth Chart (in patients up to age 18 years) (7)

Laboratory evaluation

Samples must be collected BEFORE HU therapy is initiated and at least 12 weeks after the last RBC transfusion.

a. Complete (Full) Blood Count CBC), platelet count, UNCORRECTED reticulocyte count, and WBC differential. (Calculate absolute reticulocyte count [ARC] and absolute neutrophil count [ANC])

b. Comprehensive metabolic profile, including renal and liver function tests: at least, BUN, LDH, ALT, total and fractionated bilirubin, alkaline phosphatase.

Results of these two sets of tests must be reviewed before the child is started on HU therapy.

c. Hb F studies: Hb F%, Hb F-cell % (if available) (7)(8) (16)
d. Urinalysis
e. Serum ferritin, iron, transferrin, transferrin saturation, and total iron binding capacity.
f. Parvovirus B19 IgG (if available; and, if patient is not known to be Parvovirus B19 IgG positive)
g. Serum pregnancy test for females who have achieved menarche but not menopausal. (8)

D. Monitoring of HU Therapy

Patients will be monitored through two types of outpatient visits, Interim Visits and Blood Count Visits.

1. Interim Visits:

Interim Visits will occur at 12-week intervals and will coincide with routine visits to the patient's regular SCD doctor, or nurse. During this visit, the Interim Visit Form will be completed. (19) (22)

2. Blood Count Visits:

These will occur every four weeks after initiation of HU therapy and continue until the patient has reached the TD or MD and tolerated that dose for at least eight weeks. Thereafter, these visits will occur every 12 weeks in conjunction with the Interim Visits until a change in schedule is necessitated by toxicity or other indications. (15)

The following studies will be obtained on Blood Count and Interim Visits according to the following schedule: a. CBC, diff &retic

- every 4 weeks, in patients who have not reached TD or MD for at least 8 weeks and those undergoing dose modification for hematologic toxicity, and,
- every 12 weeks, in patients who have reached and tolerated TD or MD for at least 8 weeks

b. Chemistry panel

- every 24 weeks

c. Hb F Studies (Hb F%, F-cell % [if available])

- Every 24 weeks (7)(8) (15)

E. Definition of Toxicity

1. Hematologic toxicity:

a. Absolute neutrophil count (ANC) < 1,000/µL;
b. Absolute reticulocyte count (ARC) < 80,000/µL;
c. Platelet count less than 80,000/µL;
d. Fall of 20% in Hb concentration from previous measurement or Hb≤4.5 g/dL.

2. Non-hematologic toxicities

a. Renal dysfunction as defined by a serum creatinine of 50% or more increase in serum creatinine from previous measurement;
b. Hepatic dysfunction as defined by an ALT (SGPT) value more than 2 times the upper limit of normal for age;
c. Adverse Event (See below) (7)(8)

2. Adverse Events

An Adverse Event is defined as any unwanted reaction, side effect, other clinical event in which continued HU therapy might contribute to drug toxicity or danger to the patient, or the occurrence of any of the conditions listed in the exclusion criteria. Serious Adverse Event is defined as any life-threatening toxicity or medical event occurring during HU therapy whether related or not related to HU.

F. Dose of HU

1. Starting Dose:

Children, < 18 yr.: 20 mg/kg, PO, once daily;

Adults, ≥ 18 yr.: 15 mg/kg, PO, once daily; and,

Patients with chronic kidney disease: 5-10 mg/kg. PO, once daily. (8) (15)

2. Dose escalation

The daily dose will be increased by 5 mg/kg every 8 weeks, if no toxicity occurs, until a hemoglobin level ≥ 10 g/dL is achieved or, until the maximum dose of 35 mg/kg/day is achieved, whichever comes first.

In a patient who achieves a hemoglobin level of 10 g/dL at a dose of HU < 35 mg/kg/day, and sustained over 12 weeks, that dose will be designated TD10, defined as, **the dose of HU at which a Hb level ≥ 10g/dL is achieved and maintained over 12 weeks or more**. HU dose will be maintained at that level as long as the Hb level remains ≥ 10 g/dL. The first TD10 will be designated TD10-1 and subsequent ones will be labeled TD10-2, TD10-3, etc. (8) (15)

After two consecutive Hb levels < 10 g/dL at least 4 weeks apart, following the achievement of a TD10, the dose of HU will be increased by 5 mg/kg every 8 weeks, if no toxicity occurs, until a hemoglobin level of 10 g/dL is achieved again, or until the maximum of 35 mg/kg/day is reached, whichever comes first.

The dose adjustments will be based upon the patient's weight at the time of the adjustment. This procedure will correct for changes in the patient's weight. (5)

G. Dose Modification for Hematologic Toxicity

In a patient who develops any hematologic toxicity, HU will be withheld until recovery and, blood counts will be checked weekly until recovery is complete. Recovery from hematologic toxicity is defined as ALL of the following:

- Absolute neutrophil count (ANC) 1,500/µL or higher;
- Absolute reticulocyte count (ARC) 50,000/µL or higher, if Hb is < 9 g/dL;
- Platelet count 80,000/µL or higher;
- Hb level higher than 4.5 g/dL and not lower than the most recent pre-toxicity level by 20% or more. (8) (19)

Following unilinear hematologic toxicity (see above):

a. HU will be resumed at the previous dose if recovery occurs after one to two weeks
b. If toxicity persists beyond two weeks (**sustained hematologic toxicity**), HU will be resumed, after recovery, at a dose 5 mg/kg/day lower than the previous dose (at which the toxicity occurred).
c. For patients with inadequate hematologic or poor clinical response at MTD, it is reasonable to try to increase the dose every 6 months.
d. In attempting to advance the MTD, increase dose by 2.5 mg/kg/day every 8 weeks, if well-tolerated, monitoring blood counts every 4 weeks.

Following recovery from sustained hematologic toxicity, blood counts will be monitored every four (4) weeks for 8 weeks at the reduced dose. If no hematologic toxicity recurs at the reduced dose, future dose increases will follow the regular schedule of 5 mg/kg/day every 8 weeks until the MD of 35 mg/kg/day or a TD10 is achieved. (8) (14)

If a patient shows no increase in any counts after hematologic toxicity for more than four weeks off HU, the following studies will be performed:

a. Bone marrow aspiration and biopsy will be performed to assess the state ofearly hematopoietic precursors.
b. Parvovirus B19 IgM and IgG

(if patient is not known to be Parvovirus B19 IgG positive) (8) (22)

H. Dose Modification for Non-Hematologic Toxicity and Adverse Events

For all other toxicities or suspected toxicities and adverse events, HU will be discontinued until the toxicity is resolved, the suspected toxicity is determined not to be related to HU therapy, or it is determined that the patient can no longer continue HU therapy. All adverse events and suspected toxicities will be recorded in the medical record. HU therapy will be suspended in the event of any serious adverse event or potential toxicity until it is determined that the event is unlikely to be related to HU therapy. After such a determination, HU therapy will be resumed at the previous dose. (7) (15)

I. Transfusion During HU Therapy

There will be no restrictions on blood transfusion for patients on HU therapy. In the event that a patient is transfused with red cells, however, no escalation in the HU dose will be permitted until 8 weeks following the transfusion. HU should be resumed at the pre-transfusion dose provided there are no contraindications. (8)

J. Pregnancy

Post-pubertal females on HU should be advised against pregnancy and referred to gynecologist for birth control advice. They should be asked about missed menses at every visit. In case of pregnancy, HU therapy should be discontinued. Post-pubertal males on HU should be advised against making a female partner pregnant. (22)

K. Hospitalization

Hydroxyurea therapy should be continued during hospitalization or acute illness unless the illness or its treatment is likely to increase HU toxicity. (8) (17)

L. Drug Management

Several kinds of HU are commercially available, the “original” 500 mg capsule and 400 mg, 300 mg, and 200 mg capsules under various brand names. In addition, 100mg and 1,000 mg triple-scored dispersible tablets have become available in some countries. All approved, certified brands of HU may be used for this therapy, however, whenever possible, treatment centers should limit the brands they use so that unexpected toxicities and side effects can be tracked to specific sources. Combination of formulations, when necessary, will be used in order to avoid the splitting of any capsule. Until stable HU suspension or dispersible tablets are become available for children, capsules will be compounded as suspensions by approved pharmacies, or by trained patients or parents for immediate or short-term use. HU for SCD will be ordered through regular prescriptions by ONLY certified doctors and certified pharmacies. (8) (22)

M. Management of HU Therapy

Although HU for SCD is not a research study, the implementation of HU therapy for people with SCD should be as carefully monitored as would a long-term research study. Doctors and nurses not familiar with the use of cytotoxic drugs that require close monitoring and dose modification for specific toxicities should be trained and certified to oversee HU therapy for people with SCD. Pharmacies dispensing HU for people with SCD should also be trained, certified, and approved by the treating doctors and nurses so that HU is not dispensed to patients without prescriptions and the required monitoring. (8) (15)

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