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NATIONAL GUIDELINES ON MANAGEMENT AND CONTROL OF SICKLE CELL DISEASE

INDIAN COLLEGE OF HEMATOLOGY (ICH)
THE ACADEMIC WING OF ISHBT

INDIAN COUNCIL OF MEDICAL RESEARCH (ICMR)

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E-mail: siliconmedia.ind@gmail.com, Phone: +91 9238003534

CONTRIBUTORS

- **Dr. Rabindra Kumar Jena,** Professor & Head, Clinical Hematology Dept, SCBMCH, Cuttack & Secretary, ICH
- **Dr. Haraprasad Pati,** Ex - Professor of Hematology, AIIMS, New Delhi, President, ISHBT
- **Dr. Bontha V Babu,** Scientist-G & Head, Division of Socio-Behavioural & Health Systems Research, ICMR, New Delhi
- **Dr. Manoranjan Mahapatra,** Professor & Head, Dept of Hematology, AIIMS, New Delhi
- **Dr. Vikram Mathews,** Professor Hematology Dept & Director, Christian Medical College, Vellore
- **Dr. Maitreyee Bhattacharyya,** Professor and Head, Clinical Hematology Dept, IHTM, Kolkata
- **Dr. Tuphan Kanti Dolai,** Professor & Head, Dept of Hematology, NRS Medical College, Kolkata
- **Dr. Seema Bhatwadekar,** Haemato-Oncology Care Centre, Vadodara
- **Dr. Jina Bhattacharyya,** Professor & Head, Dept of Clinical Hematology, Gauhati Medical College, Guwahati
- **Dr. Prashant Sharma,** Professor, Hematology Dept, PGIMER, Chandigarh
- **Dr. Priyanka Samal,** Professor & Head, Dept of Clinical Hematology & Hemato-oncology IMS & SUM Hospital, Bhubaneswar
- **Dr. Tulika Seth,** Professor, Dept of Hematology, AIIMS, New Delhi
- **Dr. Sunil Kumar Agarwalla,** Professor, Paediatrics, SVPPGIP, Cuttack
- **Dr. Dipty Jain,** Ex-Professor, Dept of Pediatrics, Government Medical College, Nagpur; Nodal Officer, PMO's Mission Sickle Cell Project
- **Dr. Dinabandhu Sahoo,** Team Leader, OSHSRC, National Health Mission, Odisha
- **Dr. Somanath Mukherjee,** Additional Professor, Dept of Transfusion Medicine, AIIMS, Bhubaneswar
- **Dr. Gopal K Ray,** Assistant Professor, Dept Of Transfusion Medicine, AIIMS, Guwahati
- **Dr. Damodar Das,** Assistant Professor, AIIMS, Guwahati
- **Dr. (LT Col) Neha Singh,** AIIMS, New Delhi
- **Dr. Moupali Ghosh,** Dept of Clinical Hematology, IHTM, Kolkata
- **Dr. Biswaprakash Patri,** Dept of Clinical Hematology, Gauhati Medical College, Guwahati
- **Mr. SN Agragami,** Public Health Journalist

INTERNATIONAL CONTRIBUTORS

- **Dr. Deepika Darbari,** Professor of Pediatrics, Division of Hematology, Children's National Medical Center, George Washington University School of Medicine and Health Sciences, Washington D.C., USA
- **Dr. Felicitas Roelofsen,** Germany

EDITOR:
Prof. Rabindra Kumar Jena

MEMBERS OF THE TASKFORCE FOR ICH NATIONAL GUIDELINES ON SCD

EXPERTS

DR. RABINDRA KUMAR JENA
Professor & Head, Clinical Hematology Dept, SCBMCH, Cuttack & Secretary, ICH

DR. HARAPRASAD PATI
Ex - Professor of Hematology, AIIMS, New Delhi
President, ISHBT

DR. MANORANJAN MAHAPATRA
Professor & Head, Dept of Hematology, AIIMS, New Delhi

DR. VIKRAM MATHEWS
Professor Hematology Dept & Director, Christian Medical College, Vellore

DR. MAITREYEE BHATTACHARYYA
Professor and Head, Clinical Hematology Dept, IHTM, Kolkata

DR. TUPHAN KANTI DOLAI
Professor & Head, Dept of Hematology, NRS Medical College, Kolkata

DR. SEEMA BHATWADEKAR
Haemato-oncology Care Centre, Vadodara

DR. JINA BHATTACHARYYA
Professor and Head
Department of Clinical Hematology
Gauhati Medical College & Hospital
Guwahati, Assam

DR. PRIYANKA SAMAL
Professor & Head, Dept of Clinical Hematology & Hemato-oncology, IMS & SUM Hospital
Bhubaneswar

DR. TULIKA SETH
Professor, Dept of Hematology
AIIMS, New Delhi

DR. PANKHI DUTTA
Consultant Haematopathologist
Dubai Hospital

DR. PRASHANT SHARMA
Professor, Hematology Department, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh

DR. SOMANATH MUKHERJEE
Additional Professor,
Dept of Transfusion Medicine,
AIIMS, Bhubaneswar

DR. GOPAL K RAY
Assistant Professor, Dept Of Transfusion Medicine,
AIIMS, Guwahati

DR. SUNIL KUMAR AGARWALLA
Professor Pediatrics, SVPPGIP, Cuttack

DR. DAMODAR DAS
Assistant Professor, AIIMS, Guwahati

INTERNATIONAL EXPERT

DR. DEEPIKA DARBARI
Professor of Pediatrics,
Division of Hematology,
Children's National Medical Center,
George Washington University School of Medicine and Health Sciences, Washington D.C., USA

DR. FELICITAS ROELOFSEN
Germany

EXTRA MURAL MEMBERS

DR. BONTHA V BABU
Scientist - G & Head,
Division of Socio-Behavioural & Health Systems Research,
Indian Council of Medical Research,
Dept. of Health Research, Govt. of India,
New Delhi

DR. DINABANDHU SAHOO
Team Leader, OSHSRC,
National Health Mission, Odisha

MS. VINITA SRIVASTAVA
Adviser, Health,
Ministry of Tribal Affairs
Govt. of India

DR. DIPTY JAIN
Ex-Professor and Head, Department of Pediatrics, Government Medical College, Nagpur; Nodal Officer, PMO's Mission Sickle Cell Project.

DR. PRADEEP KUMAR PATRA
Director cum Professor & Head, Dept of Biochemistry, Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh

DR. SUMAN JAIN
Chief Medical Research Officer & Secretary,
Thalassaemia & Sickle Cell Society

PULMONOLOGISTS

DR. M R PATTANAIK
Professor & Head,
Pulmonary Medicine Department
SCB Medical College, Cuttack

SOCIAL WORKER/ JOURNALIST

DR. RADHARANI SAHOO
Counselor, Sickle Cell Institute of Chhattisgarh, Raipur

MR. SN AGRAGAMI
Public Health Journalist

PATIENTS OF SCD

MS. SRADHITA SAHU
Sastri Nagar, Nayapalli, Bhubaneswar

MR. ASHISH KU. PRADHAN
Talcher, Angul

INVITED EXPERTS

DR ASHWIN VASAVA
Associate Professor,
Department of Medicine,
New Civil Hospital, Surat, Gujrat

DR ANIL KHATRI
Consultant Paediatrician, Jeevandeep Hospital.
Ahmedabad, Gujarat, India

DR DEVAPRIYA LAKRA
Professor & Head, Dept of Medicine,
JNM Medical College, Raipur, Chhattisgarh

DR NAND KUMAR MENON
Co-Founder and Former Director,
ASHWINI Gudalur Adivasi Hospital, Nilgiris, Tamil Nadu
Founder SCD Centre, Member Steering Committee,
Govt of India

DR RADHIKA SETTI
Assistant Professor, Dept of Clinical Hematology,
NIMS, Hyderabad

DR ANKIT PARMER
Consultant, Paediatric Hematology and oncologist
Healing Hands Clinic, Surat, Gujrat

DR RITA SAXENA
Associate Professor
Medicine, Gandhi Medical College, Bhopal

DR. (LT COL) NEHA SINGH
AIIMS, New Delhi

DR. ADITI GUPTA
Dept of Pediatrics, Topiwala National
Medical College & BYL Nair Charitable
Hospital, Mumbai

DR. MOUPALI GHOSH
Dept of Clinical Hematology, IHTM, Kolkata

DR. BISWAPRAKASH PATRI
Dept of Clinical Hematology,
Gauhati Medical College, Guwahati

ABOUT US

INDIAN COLLEGE OF HEMATOLOGY

The Indian College of Hematology (ICH) is the academic wing of the Indian Society of Hematology and Blood Transfusion (ISHBT). It is a conglomeration of haematological leadership in India and driven by the purpose of fostering excellence not only in academic and professional practice involving both clinical Hematology and laboratory Hematology, but also enhancing quality of health care and making it accessible to people everywhere in the country.

The ICH has a vision to standardise education, establish standard protocols for diagnosis, management and control of haematological diseases, promote research and development, and address the issues concerning academic excellence and quality of care.

It also aims to act as a national advisory body to give suggestions to NMC & NBE and allied bodies in all academic and technical activities of postgraduate education in the subject of clinical haematology and haemato-pathology; to promote nationwide collaborative research and prepare databases for various haematological diseases; to formulate the different guidelines, study groups, consensus documents, recommendations and research groups and other academic activities as assigned by ISHBT.

ABOUT US

INDIAN COUNCIL OF MEDICAL RESEARCH

Indian Council of Medical Research (ICMR), New Delhi, the apex body in India for the formulation, coordination and promotion of biomedical research, is one of the oldest medical research bodies in the world.

The ICMR has always attempted to address itself to the growing demands of scientific advances in biomedical research on the one hand, and to the need of finding practical solutions to the health problems of the country, on the other.

The ICMR has come a long way from the days when it was known as the IRFA. It is driven by the mission to generate manage and disseminate new knowledge in the medical field, focus on research on the health problems of the vulnerable, the disadvantaged and marginalized sections of the society, harness and encourage the use of modern biology tools in addressing health concerns of the country, encourage innovations and translation related to diagnostics, treatment, methods, vaccines for prevention and inculcate a culture of research in academia especially medical colleges and other health research institutions by strengthening infrastructure and human resource.

PREFACE

Sickle Cell Disease (SCD) is the most common genetic blood disease recorded in various parts of India. With variable incidence ranging from 0 to 40% depending on geographical area, it has emerged as a major public health concern in the country especially in tribal dominated pockets.

SCD contributes significantly to high infant mortality rate, maternal mortality rate and anaemia, apart from inflicting huge socio-economic burden on the people living with the disease as well as their families. Adding to woes, the community faces social stigma for the disease.

Awareness and access to health care are the cornerstone of successful interventions for management and control of any public health issue. These are severely lacking in the country as far as SCD is concerned. As a result, the people living with SCD are feeling marginalised and discriminated against.

Of late, however, things are marking a change. The Centre and state governments are realizing the public health and social impact of SCD and working towards improving health care and access for patients. New initiatives have been taken up. Due to improvement in facilities and skills of doctors, many patients are now becoming adult, getting married and going in for pregnancy.

But, despite the efforts, addressing the challenge of SCD in India is a complicated course. SCD in India has variable clinical presentation, complications and outcomes. Prediction or risk factors for morbidity and mortality are still not established. The clinical presentation with overall outcome varies among the haplo types (Senegal/ Benin/Bantu/Cameroon Vs Arab Indian Haplo type, seen in India). The management based on data of other countries may not be suitable for our patients.

Moreover, there is no uniform protocol for management of SCD in various situations of our patients based on evidence. There is, thus, a need to engage all the stakeholders to ensure holistic health care services for the entire sickle cell community with roadmap and timeline to achieve our targets.

The ICH, the academic wing of ISHBT has taken up the responsibility by preparing this SCD guideline which will be immensely benefit for the SCD community, policy makers, medical professionals, NGOs and other stakeholders.

As a nodal member, I extend my sincere thanks and appreciation to the Indian Council of Medical Research (ICMR) for joining hand with ICH to formulate and publish the first-ever national guidelines for management and control of SCD in India. This comprehensive document will be helpful in bringing uniformity in medical interventions for SCD patients while laying a foundation for control of the disease in the community-level.

I extend my gratitude to Dr Isaac Odame, Medical Director of the Global Sickle Cell Disease Network, for providing us with valuable inputs.

I offer my thanks and appreciation to all experts of Task force on SCD guideline, members of ISHBT, the sickle cell community and all stakeholders for their encouragement, cooperation and contribution to make these guidelines possible.

DR RK JENA
Editor and Nodal Officer

MESSAGE

सत्यमेव जयते

डॉ. राजीव बहल, एमडी, पीएचडी
DR. RAJIV BAHL, MD, PhD

सचिव, भारत सरकार
स्वास्थ्य अनुसंधान विभाग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय एवं
महानिदेशक
भारतीय आयुर्विज्ञान अनुसंधान परिषद
Secretary, Government of India
Department of Health Research
Ministry of Health & Family Welfare &
Director-General
Indian Council of Medical Research

MESSAGE

Sickle cell disease (SCD) is an important public health problem, and India is the second most affected nation in the world. SCD has an immense impact in terms of premature mortality and low quality of life among SCD patients.

Advances in the diagnosis, treatment and prevention of SCD have had a huge impact on the incidence and patients' health. However, timely development and implementation of cost-effective management strategies are vital to India.

I am pleased to see that the much-needed guidelines for the management of SCD have been developed by the Indian College of Hematology (ICH) of the Indian Society of Hematology & Blood Transfusion (ISHBT) in collaboration with ICMR. I am sure these guidelines will be helpful for the doctors and researchers engaged in SCD care and indirectly for alleviating SCD patients' suffering.

Lastly, I congratulate the ICH-ISHBT for this timely publication.

(**Rajiv Bahl**)

V. Ramalingaswamy Bhawan, Ansari Nagar, New Delhi-110029
Tel. : 011-26588204, Website : www.icmr.gov.in, E-mail : secy-dg@icmr.gov.in

CONTENT

1.	EXECUTIVE SUMMARY	p14
2.	MAGNITUDE OF PROBLEM & EPIDEMIOLOGY	p23
3.	SCREENING AND DIAGNOSIS	p36
4.	CLINICAL PRESENTATION	p56
5.	MANAGEMENT IN STABLE CONDITION	p61
6.	HYDROXYUREA THERAPY	p68
7.	IRON OVERLOAD & CHELATION THERAPY	p73
8.	VASO-OCCLUSIVE CRISIS ACUTE PAIN	p77
9.	MANAGEMENT OF COMPLICATIONS	p89
10.	TRANSFUSION SUPPORT	p93
11.	HEMATOPOIETIC CELL TRANSPLANT & GENE THERAPY	p98
12.	IMMUNIZATION & ANTIBIOTIC PROPHYLAXIS	p104
13.	MONITORING	p107
14.	MANAGEMENT OF PREGNANCY	p112
15.	SURGERY	p122
16.	NEWER DRUGS	p129
17.	FOOD AND NUTRITION	p134
18.	PREVENTION AND CONTROL	p138
19.	RESEARCH NEEDS: PRIORITIES & STRATEGIES	p143
20.	NEEDS OF SCD COMMUNITY: PATIENTS' PERSPECTIVE	p148
21.	ROADMAP FOR SCD IN INDIA	p150

Executive Summary [1]

Sickle cell disease (SCD), the most common inherited disorders of haemoglobin, is a monogenic disorder caused by a single nucleotide substitution at position 6 of the β-globin gene leading to polymerisation of the resulting sickle haemoglobin variant (HbS).

The Sickle variant of haemoglobin was first reported in India from Nilgiri hills among tribal population of South India in 1952. In the last 70 years, many studies and published literature have established clinical diversity among its various compound heterozygous phenotypes. SCD is now recognized as a major public health problem in the country with an increasing burden on the health care system. SCD was mainly believed to affect the tribal population of Central India, however non-tribal persons are also affected in many states such as Odisha, Chhattisgarh, Gujarat, Maharashtra and Madhya Pradesh have a significant burden of disease with a carrier frequency in the range of 1 to 44 %.Globally, some of the highest βS allele frequencies have been reported in the Indian population and India has been ranked as the country with the second heaviest burden in the world in terms of estimated numbers of babies born with the sickle β-globin gene variant (trait and homozygous births, with 42,016 (inter-quartile range, IQR: 35,347–50,919) in 2010.

The magnitude of the problem of SCD in the country is very large and diverse. Yet, despite the realization of the impact of SCD in the general population of India and its importance on public health, there is no definitive data available on theactual proportion of the population suffering from the disease nor the spread across regions and communities. Though many publications about the prevalence of disease are available for some regions, complete data at district, state and national levels are lacking. The studies reported in literature are mostly institution-based retrospective or prospective series, which are not representative of the general population hence make it difficult to draw conclusions.

As a result, persons with SCD have not only been deprived of timely detection in a majority cases, but also, overall have been left out of adequate and specialized health care. They have been deprived of the advances and developments in diagnosis, treatment and adequate management so as to lead their lives optimally – with dignity and achieving the best potential. While there is inequity in health care system, medical advances that can bring more relief to the SCD patients have not been made accessible to them. Thus, a major chunk of the patients continue to live with serious unmet medical needs.

Along with unmet health care needs, people living with SCD are also forced to battle social discrimination and stigma all their lives. This social attitude towards people living with SCD is due to lack of awareness about the disease among the communities. A major contributing factor is absence of dedicated health care delivery system which is accessible to all those suffering from the disease, lack of focus of the government, administration, public advocacy groups, lack of social support mechanisms, public education and community sensitisation about SCD as a preventable, treatable and manageable disease.

Thus, there is an urgent need to focus on recognising the important public health burden of SCD in the country and organise and restructure health care system to make high quality SCD service delivery universally accessible to people regardless of where they live.. This has to include major aspects:

1. Nationwide registry built on a robust population screening exercise.
2. Improvement of health care infrastructure and its extension to primary care settings.
3. A uniform nationwide standard protocol for diagnosis, treatment, management and monitoring of patients.
4. Patient education and community engagement.
5. Establishing support systems dedicated to SCD at all levels of the health care system.

[1] Citations and references are included in the specific chapters of these guidelines document

NATIONAL GUIDELINES ON MANAGEMENT AND CONTROL OF SCD IN INDIA – A BEGINNING

In a bid to achieve this goal, the Indian College of Haematology (ICH) of the Indian Society of Haematology and Blood Transfusion (ISHBT) has sought to formulate a National Guidelines on Management and Control of Sickle Cell Disease in India that aims to not only standardise diagnosis, treatment and care of people suffering from SCD in India, but also sets a larger objective of bringing multi-sectoral engagement including governments, health care professionals, allied sectors, public health organisations, NGOs and patients groups to improve the health of people living with SCD by making quality care that addresses all aspects of SCD accessible.

For formulation of the guidelines, a national taskforce comprising top experts from the field of haematology was formed in early 2022. The core body held multiple sessions to deliberate on different aspects and form consensus on preparing a comprehensive document on SCD care in India along with a roadmap with specific time-frame for effecting drastic improvement in SCD care delivery, accessibility and social attitudes.

This document is the outcome of the rigorous exercise over the last several months and has been finalised by achieving consensus among the experts. The taskforce has presented its recommendations on each and every aspect of SCD in India, all of which have been evaluated based on the best evidence. Where the evidence is weak, the recommendations have been based on consensus among the experts..

This guidelines document is the first-of-its-kind of initiative in the country. It is the most comprehensive document on SCD in India, addressing all aspects of the public health problem.

Below are presented some of the major aspects addressed in the document along with the recommendations:

DIAGNOSIS AND SCREENING

This section outlines the laboratory investigations and tests available for diagnosis and screening for sickle cell disease (including HbSS, HbS/β^0or HbS/β^+thalassemia, HbSE, $HbSD^{Punjab}$ and HbSC diseases, etc.) as well as the carrier state. It aims to provide laboratory and clinical haematologists with an evidence-based background to scientifically select the most appropriate and feasible laboratory test option(s) in various Indian practice settings. Important considerations in test performance and interpretation are included wherever relevant.

RECOMMENDATION:

1. Test selection, performance and reporting must always be tailored to the necessity of the state, healthcare setting and testing scenario.
2. All screen-detected cases of sickle cell disorders should be subsequently confirmed by a diagnostic test using an independent technology.
3. Point-of-care rapid tests like paper-based haemoglobin solubility assays and immunochromatographic lateral flow assays are suitable for screening followed by confirmation using standard assays like CE-HPLC/A-CZE.
4. Parental studies of haemogram and CE-HPLC or A-CZE are invaluable in resolving diagnostically difficult cases, even when genetic analyses are available.
5. Discovery of a proband with a clinically significant haemoglobinopathy must prompt the clinical advice to screen as many blood relatives as feasible for haemoglobinopathies. This enables detection of further asymptomatic carriers who can then participate in informed reproductive decision-making at the appropriate time points.
6. For settings lacking CE-HPLC or A-CZE, a minimal integrated screening panel combining tests for HbS (sickle solubility test, or paper-based haemoglobin solubility assays), β-thalassemia (hemogram analysis for microcytosis, i.e., MCV ≤80 fL and/or MCH ≤27 pg) and, in high frequency regions, red cell indices or the dichlorophenolindophenol (DCIP) test are recommended.

7. Molecular genetic studies are rarely required in routine clinical practice but mandatory for prenatal testing. These can help resolve confusing cases, especially post-transfusion, or if parental studies are not available.

CLINICAL PRESENTATION

A patient with SCD will most commonly present with varied clinical manifestations such as persistent pallor, pain, fever, lethargy and jaundice. Sickle cell disease may present with acute and chronic complications. Major chronic manifestations are chronic pain, anaemia, neurological deficits or seizure disorder, pulmonary conditions including pulmonary hypertension, renal impairment, osteoporosis, bone infarction, cardiomyopathy with diastolic dysfunction, hepatotoxicity and pigmented gallstones, chronic leg ulcers and proliferative retinopathy.

OBSERVATIONS

- Considerable heterogeneity of clinical manifestations of SCD India.
- Most common complication of SCD is an acute episode of severe pain referred to an acute VOC.
- Approximately 50 to 80% of hospitalization in SCD are due to VOC.
- The age at first clinical presentation varies from 1 month to 5 years.
- Anaemia in Indian SCD children is multifactorial. Nutritional deficiency (iron, Vitamin B12 folic acid deficiency), malnutrition, infections and parasitic infestations are common.
- Indian SCD patients continue to have splenomegaly during the second decade of life.
- The prevalence of acute chest syndrome in Indian SCD was not well established by studies.
- Neurological complications are common among Indian patients and seen <20 years of age.
- Pulmonary hypertension is prevalent in over 1/3rd of the pediatric patients.

MANAGEMENT IN STABLE CONDITION

Sickle cell disease encompasses different states which may be acute and chronic or stable. The problems that can arise during stable conditions include chronic pain which can affect the day to day life of the patient including absence from school and from work, infections, deficiency disorders and others.

RECOMMENDATION:

1. Hydroxyurea should be started in all age groups at the dose 10 mg/kg/day irrespective of clinical condition. If required, the dose can be increased by 5 mg/kg/ every 8weeks till MTD or up to dose of 35 mg/kg/day.
2. The dose should be titrated to maintain ANC of minimum 1500 per microL and PLT of >80,000 per microL.
3. Young females willing for pregnancy should discontinue hydroxyurea after discussion with their physicians. However it can be continued in selected cases if required after 1st trimester of pregnancy.
4. Newer drugs for VOC (pain crisis) and other pharmacological agents used for pain relief like paracetamol, pregabalin, triptiline,etc., should be tried when there is sub-optimal response to base level pain or intolerance to hydroxyurea.
5. Folic acid, vitamin D, calcium and zinc supplementation in all cases.
6. Iron supplementation if there is evidence of iron deficiency anaemia
7. Fever or any other infection is to be treated as medical emergency and penicillin prophylaxis should be given to children.

IRON CHELATION

RECOMMENDATION:

1. Sickle cell patients with Arab-Indian haplo type are the main category seen in India. The predom-

inant phenotype is vaso-occlusive and thus iron overload requiring chelation is not required in most of the cases.
2. Iron overload is possible in SCD and should be considered if anyone of the criteria is fulfilled - SF is > 1000 ng/mL , LIC is > 3.5 mg/g dry weight, received 10 transfusion or cumulative transfusions of > 120 mL of packed RBCs/kg or if the cardiac T2* is 8 ms or less aggressive chelation is indicated.
3. Deferasirox at the dose 20 to 40mg/kg/day is the preferred agent.
4. Combination of Depeferasirox and Deferiprone may be considered if the serum ferritin level is not controlled with DFX alone or there is a need of potentiating the iron chelation due to the iron overload in various organs.

VASO-OCCLUSIVE PAIN MANAGEMENT

Acute painful sickle cell episodes occur unpredictably, often without clear precipitating factors. Their frequency may vary from less than one episode a year to severe pain at least once a week. Pain can fluctuate in both intensity and duration, and may be at times excruciating. Nearly all individuals affected by SCD will experience a VOC during their lifetime. Recurrent episodes may lead to irreversible damage to organs. The majority of painful episodes are managed at home, with patients usually seeking hospital care only if the pain is uncontrolled or they have no access to analgesia. Goal of efficient VOC management is not only faster pain control but prevent tissue damage from ischaemic injury.

RECOMMENDATION:

1. VOC pain in SCD should be controlled aggressively with adequate analgesics like tramadol, paracetamol, NSAIDs, diclofenac (if no contraindication) and regional Anaesthesia depending on case to case basis.
2. Opoids and buprenorphin patch should be considered in severe cases not responding to conventional analgesic with precautions to prevent addiction as mentioned earlier.
3. Other adjuvant therapies like management of fluid, electrolyte, oxygen saturation may be helpful.
4. The medications/adjuvant interventions recommended during stable condition should be continued.
5. Steroid should not be used during VOC stage.
6. Reduction of HbS level below 30-50% by exchange transfusion (simple/red cell apheresis) could be an effective modality in reducing pain in resistant / recurrent VOC.

MANAGEMENT OF COMPLICATIONS

The complications of SCD can be acute (vaso-occlusive crisis, sequestration crisis and aplastic crisis, haemolytic crisis, etc.) and chronic (involving almost all organs).

RECOMMENDATION:

1. Regular monitoring should be done to detect any chronic complications/organ damage at early stage.
2. Management of specific organ involvement should preferably be multi-disciplinary approach and the interventions are outlined above.
3. Comorbidities like diabetes, hypertension, renal dysfunction and cardio-respiratory illness, etc., can deteriorate the Sickle-related organ damage and thus should be managed aggressively.
4. Disease modifying therapy like HU and blood transfusion (wherever indicated, with extended crossmatching should be considered along with the specific treatment.

BLOOD TRANSFUSION IN SCD

Transfusion support in SCD depends on the clinical condition and feasibility and is of three methods - Simple Transfusion (ST), Manual Red Cell Exchange (M-RCE) and Automated Red Cell Exchange (A-RCE).

RECOMMENDATION:

1. Transfusion should be done only when it is needed and cannot be managed by alternatives. Red cell transfusion if needed should be selected as per the antigen profile as mentioned below.
2. Red cell antigenic profile should be performed at the earliest opportunity, optimally before 1st transfusion. It includes minimum Rh (D, C, c, E, e), and Kell. It is preferable to include Duffy, Kidd, and MNS especially if there is already development of allo-antibodies.
3. An extended red cell antigen profile by genotype or serology over only ABO/RhD typing for all patients.
4. **Red blood cell of choice for transfusion in ST and RCE:** At least Rh, Kell matched, and preferably Duffy, Kidd, and MNS matched donor blood unit, leuko reduced, sickle cell negative, and less than 7 days old, and AHG cross matched compatible unit, should be selected for transfusion.
5. Antibody screening should be included in pre-transfusion testing of previously transfused patients.
6. The management of post-transfused haemolytic reaction should be done with IVIG, high dose of EPO and other supportive therapy.
7. High risk patients (who have already developed allo-antibodies) who need blood transfusion as life saving procedure should receive prophylactic Rituximab.

MONITORING

As the sickle cell disease is more prevalent in tribal areas of India in various states across the country, a uniform guideline should be practiced in managing as well as monitoring the patients. This should include regular annual monitoring of cerebrovascular disease, cardiovascular disease, pulmonary complications, renal and hepatic complications, blood transfusion, hydroxyurea treatment, etc.

PREGNANCY

Pregnancy with SCD is of high risk category with increased maternal complications such as anaemia, VOC crises, acute chest syndrome, jaundice, maternal mortality, pre-eclampsia, urinary tract infections, etc. There is paucity of evidence to recommend the management of SCD in pregnancy and vice versa due to lack of adequate randomized controlled trials. However, the following recommendations are based on available data, extrapolation of the evidences and consensus expert opinion.

RECOMMENDATION:

1. The women with SCD and their husband should accept pregnancy on their own risk as there are no reliable predictors of the risk, morbidity and mortality related to pregnancy.
2. All women with SCD should undergo with partner testing prior to the initiation of pregnancy.
3. High risk couples (both carrying the Hb Pathies genes) should be counselled for reproductive options, prenatal diagnosis or pre-implantation genetic diagnosis (PGD).
4. All women should be examined and managed by necessary special investigations as per the need prior to the pregnancy.
5. Folic acid: 5 mg daily to all women before conception and throughout pregnancy.
6. Vitamin D & calcium supplementation may be considered if there is no contraindication.
7. Terratogenic drugs like ARBs, ACEi should be replaced with safer drugs.
8. Hydroxyurea should be discontinued 3 months prior to conception.
9. Iron chelators should be stopped before conception and throughout the pregnancy.
10. Iron overload should be treated preferably before conception.
11. Iron supplementation for women having evidence of iron deficiency throughout the pregnancy like that of others.

12. Injectable methylcobolamine or other legitimate preparation should be given in the usual dosage before and throughout pregnancy.
13. PND @ 12 weeks followed by continuation or termination of the pregnancy if the fetus is likely to be healthy or diseased respectively. Antenatal care should be provided by a multidisciplinary team including an obstetrician, haematologists and other specialists.
14. Low dose aspirin: 75 – 150 mg per day from 12 weeks of gestation. Should be reviewed at 36 weeks of gestation to considered stopping.
15. If needed transfusion should be given; ABO-compatible, extended Rh- and Kell matched, CMV Negative and HbS Negative. If there is any presence of red cell antibodies in the patient then the donor red cell should be negative for the corresponding antigen.
16. NSAIDs should be used with caution in 1st trimester and avoided after 31st weeks of gestation.
17. LMWH should be given to all women at usual dosage presenting with VOC or during any antenatal hospitalization.
18. Normal growing baby should be delivered between 38 – 40 weeks of gestation

SURGERY

Patients with SCD are referred for surgery at some point in their life time. Surgical complications are more common in patients with SCD compared to the general population due to their increased risk of post-operative acute chest syndrome, infections, vaso-occlusive pain crises and 30-day surgical mortality. Surgery in patients with SCD is associated with increased riskof Sickle-related complications (painful crisis, acute chest syndromes, renal insufficiency, stroke), increased post-operative complications (25-30%) and increased peri-operative mortality (1.1%). Careful pre-operative assessment and judicious peri-operative management are critical in mitigating these risks. Routine surgery should be avoided if patient is febrile and having a painful crisis.

RECOMMENDATION:

Pre-operative Evaluation

1. Pre-operative optimization is a multidisciplinary process that involves a haematologist with SCD expertise, an anaesthesiologist, transfusion specialist and the surgical team.
2. Routine surgery should be avoided if patient is febrile and having a painful crisis.
3. Before proceeding for surgery, the treating physician should assess to:
4. Determine whether all conservative measures have really failed .
5. Determine the need for surgical procedure.
6. Consider the risks associated with surgery vs continuing with conservative management.
7. Explore lesser invasive options.
8. Determine whether surgery will allow them to achieve their personal goals and improve the quality of life.
9. The patient's history of strokes, acute chest syndrome, obstructive sleep apnea, adverse reactions to sedation, or recurrent VTE should be documented since these parameters increase the patient's risk of peri-operative complications.
10. For those with high baseline haemoglobin (above 9 g/dl), perhaps exchange (or partial exchange) transfusion, rather than simple transfusion, should be used to avoid raising the haemoglobin level above 10g/dl.
11. The transfusion plan should be patient-specific and take into account the SCD genotype, baseline haemoglobin, disease severity, risk classification of the surgery, and history of prior surgical complications.

Intra-operative period

1. The most important factor to consider intra-operatively is to avoid imbalances in volume status,

temperature, acid-base balance, blood pressure, and oxygenation, since derangements on above parameters increase red blood cell sickling, which can result in acute organ injury.
2. Practical strategies to maintain euvolemia include avoiding prolonged fasting prior to surgery without IV fluids, monitoring fluid intake and output, and decreasing IV fluids as soon as patients are able to maintain adequate oral fluid intake.

Post-operative period

1. Regular monitoring and treatment of infection.
2. If oxygen saturation falls by ≥2% below the patient's baseline or is ≤94%, it is necessary to give supplemental oxygen and to evaluate the patient with consideration for post-operative complications such as acute chest syndrome and pulmonary embolism.
3. Routine incentive spirometry to reduce the incidence of atelectasis and acute chest syndrome.
4. Post-operative pain management can be planned s, often similar to a patient's usual inpatient acute pain plan and including patient-controlled analgesia.
5. Adequate deep vein thrombosis prophylaxis must be instituted.

CURATIVE OPTIONS – BMT, GENE THERAPY

Current treatment options, such as hydroxyurea and regular transfusion therapy for the disease, only ameliorate the disease severity rather than actually curing it. In light of this, an allogeneic hematopoietic cell transplant (allo-HCT) is the only treatment strategy that is widely available in the country and can actually cure this disease. More recently there is increasing excitement on the prospect of gene therapy becoming a one-time curative procedure for patients with sickle cell disease. There are different strategies being adopted for gene therapy in sickle cell disease and early phase clinical trials appear to be promising.

RECOMMENDATION:

1. SCD patients who are manageable with standard therapy should continue with their treatment regimen.
2. Allogenic BMT may be considered in a sub-set of high risk patients with anyone of the complications/indications discussed above.
3. Myeloablative conditioning regimen with Busulfan, Cyclophosphamide and ATG are preferred.
4. Pre and post BMT management should be as per SOPs.
5. Gene therapy looks realistic, which may be available in near future.

NEWER DRUGS

In recent years (2017-2019), FDA has approved three new medications for management of this disease along with hydroxyurea which remains standard of care for individuals with sickle cell anaemia. They include L glutamine, Crizanlizumab, Voxelotor, etc. Besides these FDA approved drugs, there are various novel agents based on different mechanism of action which are being studied for sickle cell disease. The agents targeting adhesion includes Rivipansel, IVIg, Savuperin which acts by either selectin inhibitor or disrupts neutrophil mediated sRBC capture. Others like arginine, citrulline, N acetylcysteine, omega3 fatty acids act by preventing inflammation by reducing oxidative stress and decreased formation of reactive oxygen species. Novel agents are being studied for inducing HbF includes Decitabine, Metformin among others. Antiplatelets, anticoagulants like Rivaroxaban, Apixaban, unfractionated Heparin are also being studied. Novel opioid sparing agents are in trials for managing painful crisis including Buprenorphine, Ketamine, Gabapentin, Momentin.

RECOMMENDATION:

1. The FDA approved newer drugs for sickle cell disease had different mechanisms of action than hydroxyurea and have minor adverse effects.
2. These drugs can be considered along with hy-

droxyurea as a possible option to reduce complications in sickle cell disease.
3. Adherence to disease modifying therapies is important to reduce complications related to SCD.
4. Crizanlizumab may be beneficial in reducing the number of hospital visits associated with VOCs.
5. Reduction in the cost of these newer drugs may lead to increased use as treatment options for sickle cell disease.

PREVENTION AND CONTROL OF SCD IN INDIA

India has the main reservoir of Hbpathies like SCD and Thalassemia in the entire world, whose prevalence is high and varies from 5 to 30% depending on the geographical area. It has a huge socio-economic burden and contributes significantly to IMR and MMR and anaemia. SCD, Thalassemia and haemoglobin diseases are three major HbPathies seen in different parts of India. Thus, a control of HbPathy is utmost essential. For logistic and financial realistic point of view, it is imperative to integrate all types of Hbpathy in one programme as the patients, the blood sample, the equipment and human resources are the same. The short-term goal is to reduce haemoglobinopathies by 5% in 5 years.

RECOMMENDATION:

1. Prevention and Control of SCD along with other haemoglobinopathies are cost-effective, beneficial and realistic.
2. Affordable and accessible holistic health care system will improve the morbidity and mortality, and regain the confidence of SCD community. This will help in eradicating the social stigma which is essential for effectiveness of any control programme.
3. This guideline has outlined the framework of control and prevention programme. However, the Government of India/State governments should formulate their programmes considering their specific needs.
4. Haemoglobinopathies are associated with anaemia in significant percentage of cases. Thus, the Taskforce unanimously feels that the national anaemia programme should be integrated with Haemoglobinopathies programmes.
5. The data system should be robust and secured. It can be integrated to create a national database.

RESEARCH NEEDS IN SCD

Although a considerable number of studies were carried out in India, they are mostly limited to screening, and some are extended to molecular typing of Hb S. very few clinical and interventional studies are available. The Indian studies available so far have very fewer implications on practice, particularly in the prevention and management of the disease. Thus there is a huge unmet medical need which urgently requires addressing with intensive research in the field. The research should encompass all aspects of SCD: Screening/Surveillance/Registry /Understanding the natural history; Clinical research, Treatment and management, Equity in care, Health care models, Physical, social and economic impact of SCD, etc.

ROADMAP FOR THE NEXT DECADE

Recognising SCD as a major public health issue and concern at the national and state-level is the first step towards combating the disease in the country. While there is inequity in health care system, medical advances that can bring more relief to the SCD patients have not been made accessible to them. Thus, a major chunk of the patients continue to live with serious unmet medical needs. Along with the excruciating suffering from the affliction, the patients also have to battle social stigma. Thus, a strategic plan with roadmap for holistic implementation of SCD community in the country is the need of the hour.

A strategic plan and a defined roadmap are required to make this possible. The plan should be based on the seven fundamental pillars – **Identification, Accessibility, Efficient, Quality, Safe, Equitable and Empowering.**

- **STRATEGY-1: Identification (Timeframe 3-5 years):** SCD registries should be initiated in a comprehensive manner

both at the hospital and population-level. This will help in studying the epidemiology and burden and also evaluating the outcomes of interventions on the ground. It will guide formulation and implementation of an effective national plan for prevention and control of SCD in India.

- **STRATEGY -2: Accessibility (Time frame 3-5 years):** Comprehensive care centres with necessary infrastructure, human resources and facilities should be made available across the country which should be affordable as well as accessible. Laboratory infrastructure should be improved at the primary health care level for early detection of SCD. Referral facilities should be strengthened at DHH level to manage SCD. A module for training of doctors and health care givers and ICE matter for patients and public should be designed.

- **STRATEGY – 3: Efficient (Time frame 2-4 yrs):** Apart from increasing the number of doctors in speciality care, there is an urgent need to enhance SCD management capabilities among personnel posted at the primary care-level as well as general physicians in the community. Comprehensive training should be given to all doctors posted at PHCs, CHCs, SDHs, DHHs, etc, which are the primary point of care for all SCD patients. Laboratory and nursing personnel at the grassroot level should be trained for SCD. All involved caregivers should receive periodic training with skill-upgradation to keep up with advances and changes in SCD care.

- **STRATEGY 4: Quality (Time frame 2-3 years):** Quality and efficiency of SCD care can only be achieved through constant monitoring at every level. A third party should be involved in conducting research to assess the quality of the available health care, its gaps and solutions thereof. ICMR, other independent organisations can be involved for such activities. The recommendations should be studied and acted upon in a timely manner so that improvements can be made for the benefit of the patients as well as enhancing strategy planning.

- **STRATEGY 5: Safe (Time frame 2-4 years):** Establishment of Centres of Excellence (CoE) with research activity and allocation of funds for the purpose. There should be at least, two CoEs in each state. The CoE will function as referral centre for overall management of complicated/undiagnosed SCD cases. They will be responsible for training of health care professionals, allied personnel, modify the SOPs depending on the advances and changes in care systems, ensure establishment of new technology and services in centres as per the need and provide technical advice to govt and other related agencies.

- **STRATEGY 6: Equitable (Time frame 3-5 years):** SCD care in India should integrate holistic awareness generation programme along with strengthening advocacy which will not only educate the persons with the disease but also sensitise the society on this crucial public health issue. Governments, health care providers, social organisations, all stakeholders and media should be involved in creating awareness about SCD. Special campaigns should be launched to sensitise the general communities on SCD regarding the availability and utilisation of holistic health care facilities and break the social taboos and end discrimination of the sufferers. Collaborative efforts among advocacy groups, NGOs, community leaders, teachers and students, etc., should be strengthened for generating awareness.

- **STRATEGY 7: Empowering (Time frame 2-3 years):** Persons with SCD should be empowered with all support systems to lead a normal life with dignity and freedom. All social stigma and taboos attached with SCD should be eradicated through sustained efforts to address the myths and misconceptions around the disease. Mission mode campaigns should be launched with the aim of eradicating social stigma around SCD. Education, vocational, rehabilitation, skill-development initiatives to be strengthened for empowering persons with SCD to lead a dignified life.

CHAPTER 1

Magnitude Of Problem & Epidemiology

Sickle cell Disease (SCD) is a monogenic disorder caused by a single nucleotide substitution at position 6 of the β-globin gene leading to polymerisation of the resulting sickle haemoglobin variant (HbS). The most severe form is the symptomatic homozygous sickle cell disease, which results from the inheritance of two copies of the sickle β-globin gene variant (SS). Individuals with mutation on one gene are called sickle cell traits/ sickle cell carriers and are clinically asymptomatic, however sickle shaped RBC's can be demonstrated in their blood film. Though clinically the sickle trait persons do not manifest disease they are important to recognize as the high prevalence of carriers is an important assessesment and will give rise to higher burden of births of patients with homozygous sickle cell disease. Hence identification of the sickle cell carriers has public health implications for awareness and prevention programmes.

THE BURDEN OF SCD IN INDIA

Sickle variant of haemoglobin was first reported in India from Nilgiri hills among tribal population of South India in 1952. In the last 70 years, published literature has established clinical diversity among its various compound heterozygous phenotypes. SCD is now recognized as a major public health problem in the country with an increasing burden on its health care system. SCD was mainly believed to affect the tribal population of central India, however non-tribal persons are also affected in many states such Odisha, Chhatisgarh, Gujarat, Maharashtra and Madhya Pradesh show a burden of disease with a carrier frequency in the range of 1 to 44%.[1-4]

Globally, some of the highest βS allele frequencies have been reported in Indian populations [2-4] and India has been ranked the second worst affected country in terms of predicted sickle β-globin gene variant (trait and homozygous births, with 42,016 (interquartile range, IQR: 35,347–50,919) babies estimated to be born with SCA in 2010.[5]

The Ministry of Tribal health is undertaking screening and this initiative is an important beginning. The district-wide data from 16 States most impacted by the high prevalence of sickle cell disease is important for public health policy planning, some data has already been collected and further screening is being conducted. Once completed in all affected districts this will be an invaluable resource.

Limitation of the present available data: The magnitude of the problem of SCD in the country is very large; the discussion on magnitude is impeded by the lack of a population-based registry. Though many publications about the prevalence of disease are available for some regions, complete district-wise national data is lacking. The studies reported in literature are mostly institution-based either retrospective or prospective compilation of consecutive cases, which are not representative of general population hence make it difficult to draw conclusion. The paucity of community-based surveys and variability in the methodology followed in the published prevalence studies make it difficult to draw comparison between the states. Also, the available community-based surveys are from different time periods, because of migration and inter-marriages, the data may not reflect the picture as of today.

The target population and testing methods also vary between studies and hence the comparison of prevalence data between different states is not possible. The screening test used in earlier studies was only solubility test which does not differentiate between sickle cell trait and disease.

With the understanding that the published data is incomplete, we have still undertaken the task to compile and present some of the most recent published literature from various parts of the country and present the current situational analysis of Sickle cell disease and trait in the country. We have also presented district-wise distribution of sickle cell trait as it is more relevant for the purpose of prevention. The legend scale of the figures are specific to each state and not comparable between states due to the above mentioned

lacunae.

SCD has varied spread from indigenous groups to other communities and now an overall reported prevalence of 4.3% in India. Heterogeneous distribution of Sickle haemoglobin (HbS) has been documented in diverse parts of India with a high prevalence in states Gujarat, Maharashtra, Madhya Pradesh, Chhattisgarh, Odisha, Jharkhand and Telangana. We describe below the current data (published and few unpublished data shared) on epidemiology of Sickle Cell haemoglobin in various regions/ states of India.

WESTERN INDIA

Gujarat: Gujarat state is known to have 12 tribal districts with 89.12 lakh (14.7%) tribal population. The estimated number of SCT cases is at least 9,00,000 (10%) and that of SCD is 70,000 (0.75%) in the state.[6] The *Dhodia, Dubla, Kukna, Gamit, Chaudhary, Halpati, Varli, Kokni, Kathodi, Kolcha, Kotwadia*, etc. are major tribes in Gujarat with documented prevalence of HbS.[7-11] The *Dhodia*, *Dubla*, *Gamit*, and *Naika* tribes are particularly reported to have a high prevalence of HbS in the range of 13-31% . [12] The reported prevalence of SCD ranged from 0.6% to 35%, however it cannot be generalized as studies have adopted different methodologies with different approaches and different classification of castes and target population.[13] Fig 1. presents the prevalence of sickle cell trait derived from district-wise pre-marital screening programme of Gujarat conducted from 2004–2022 (unpublished data).

An extensive population survey has been done by the Indian Red Cross Society, Gujarat State Branch where 1,68,498 tribals from 22 districts were screened and the overall prevalence of sickle cell carriers was 11.37% among tribal areas and 1.1% among non tribal areas.[14,15] Some tribal groups in south Gujarat like *Chaudry*, *Gamit*, *Rohit*, *Vasava* and *Kukana* have shown both a high prevalence of HbS (6.3 to 22.7%) as well as β-thalassaemia trait (6.3 to 13.6%). These tribal groups would have the likelihood of co-inheriting both these genes.[16-17]

In a voluntary community screening programme, from rural south Gujarat, using a newer HPLC methodology for confirmation of diagnosis, a prevalence of SCT (15.63%) in *Choudhary* labeled as general caste (non-tribal) against 18.5% in *Rathva* (ST sub-population) was cited , while the prevalence of 2.3% for SCD was documented using panel data methodology.[18]

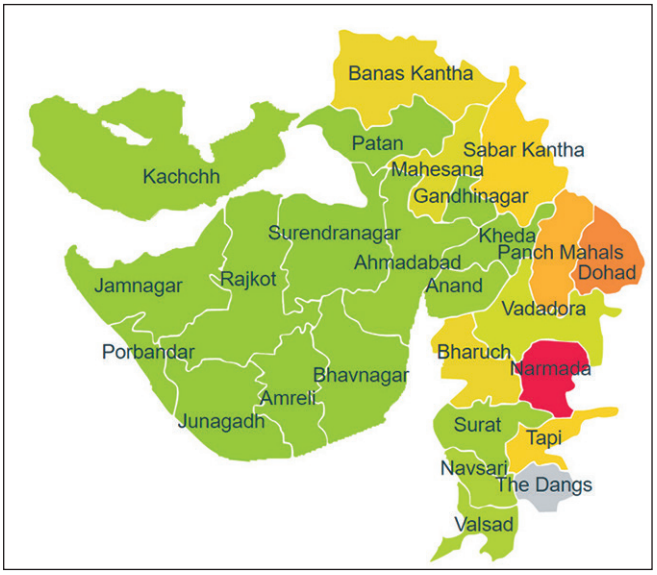
Another larger community-based study based on camp approach screened 32,857 samples of students from different schools and colleges in South Gujarat, which found that the overall prevalence of BTT and SCT was 4.4% and 1.3% respectively. The study also documented *Gamits, Vasavas, Mayavanshi, and Chaudhary* as the most commonly affected subcastes. The study documented prevalence of SCD among *Mayavanshi* subcaste (6.9%), which is not documented in any other published literature. Other prevalence studies among adolescents and medical undergraduates suggest the range of SCD from 12.7% to 37.5%. However, as these students were institutional-based, they do not reflect the community-level prevalence.[19]

A recent study analysed the tribal maternal admissions, in the community-based hospital of SEWA Rural (Kasturba Maternity Hospital) in Jhagadia block, Gujarat from 2011 to 2015. The study reported 1.2% of tribal delivery admissions were homozygous for sickle cell disease and 15.6% of tribal delivery admissions had the sickle cell trait.[20]

Newborn screening programme in South Gujarat reported results of 5467 newborns, using HPLC, with diagnosis by molecular analysis, across four districts of South Gujarat over 2 years. There were (0.60%) babies identified as sickle homozygous, and (0.23%) had sickle-β-thalassaemia; 12.5% were identified with sickle cell trait. 0.23% of SC homozygous condition. The highest proportion of births with sickle cell trait was found in the *Warli* tribe (22.9%), followed by the *Bhils* (21.7%), *Chaudharys* (20.0%), and *DhodiaPatels* (18.5%). The proportion of births with sickle cell anaemia was highest among the *Dhodia Patels* (1.54%). [21] The same programme adopted a targeted screening approach with HPLC test employed to test newborns of ante natal women found positive on solubility test. As a result of targeted screening, 3.5% of the newborns were diagnosed with HbS and started on the preventive penicillin treatment.[22]

FIG 1 : DISTRICT-WISE PREVALENCE OF SICKLE CELL TRAIT REPORTED FROM PREMARITAL SCREENING PROGRAMME

Conducted from 2004-2022



The range of prevalence is 21.45% - 0.31% from premarital screening programme and legend is not comparable to other states

Maharashtra: From initial studies, it was reported that sickle cell gene is widely spread in all districts of eastern Maharashtra (known as Vidarbha region), North Maharashtra (Satpura ranges), and some parts of Marathwada region.[23-24] The prevalence of sickle cell carriers in different tribes varies from 0 to 35%. The tribal groups with a high prevalence of HbS (20-35%) include the *Bhils*, *Madias*, *Pawaras*, *Pardhans* and *Otkars*. It has also been estimated that Gadchiroli, Chandrapur, Nagpur, Bhandara, Yoetmal and Nandurbar districts would have more than 5000 cases of sickle cell anaemia.[25]

A study conducted to find out the prevalence of sickle cell genes in the tribal population in rural area of Palghar district from August 2015 to August 2017 screened almost 5000 subjects. 1% sample was found to be affected by sickle cell disease (HbSS) and 4.08% were sickle cell heterozygous (HbAS). The subjects in the study belonged to schedule tribes (*Warli, Kakari, Malhar Koli, Dhor Koli Vanjari, Wadwal*) and schedule caste (*Buddhist and Mahar*).[26]

Another study based on a *cross-sectional* sample, randomly collected and analysed from 294 individuals (165 male and 129 female) in different rural areas of Chandrapur district of *Maharashtra.* The population was screened by solubility test followed by electrophoresis and prevalence of sickle cell anaemia was found to be 18.3%.[27]

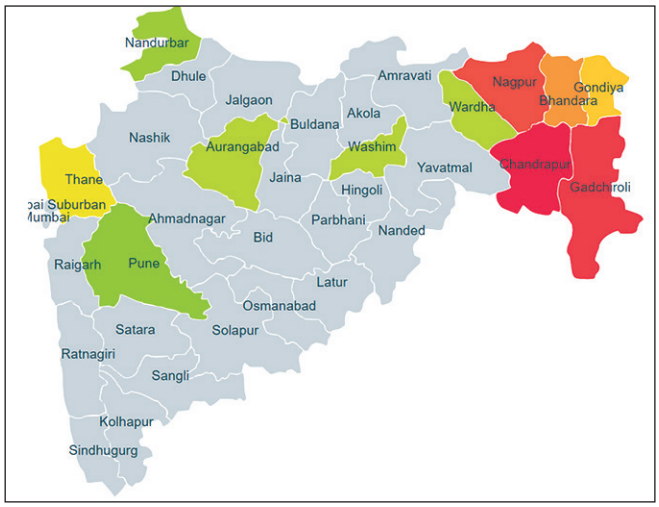
A systematic mass screening was carried out in various schools and at the community level in four districts of Vidarbha region of eastern Maharashtra. A sample from pre-marital age group were screened for haemoglobin S and haemoglobin βT using solutions of qualitative solubility test and NESTROFT, respectively. It was observed that 6.4% individuals were positive for HbS and 2.1% for HbβT. The frequency for HbS and HbβThalassaemia varied between 0-33% and 0–10%, respectively, among the studied populations. A very high frequency of HbS was encountered among the *Bais* (33.3%) the *Pardeshi* (25%), the *Pardhan* (23.8 %) and the *Marar* (20.4 %). A moderate HbS frequency was observed among *Dhiwar* (12.8%), *Gond* (12.4%), *Shimpi* (11.1%), *Mahar* (10.9%), *Madgi* (10.0%), *Khairekunbi* (9.3), *Bania* (9.1%) the *Zadekunbi* (7.7%), and the *Gowari* (7.3 %). Significant frequencies of HbS were also observed among the *Banjara* (5.9%), the *Dangekunbi* (5.6%), the *Kunbi* (4.9%), the *Telugu* (4.8%), the *Kalar* (4.7%), the *Bawanekunbi* (4.3%), the *Brahmin* (4.2%), the Muslim (3.7%), the *Tiralekunbi* (3.6%) and the *Teli* (3.2%). The range of HbS gene frequency of 1-3 per cent was accounted for the *Chambhar*, the *Dhangar*, the *Dhobi*, the *Halba*, the *Kohali*, the *Lohar*, the *Maratha kunbi*, the *Mehetar*, the *Powar* and the *Rajput* of eastern region of Maharashtra.[28]

The community-based descriptive cross-sectional survey was conducted in urban parts (cities and towns) of Amravati, Bhandara, Chandrapur, Nagpur and Yeotmal districts of East Maharashtra using screening camps arranged in schools, community halls. A total of 4.94% individuals were found to be positive for sickle cell disorder,

of which 3.88% with heterozygous genotype and 1.06% with homozygous genotype. Bhandara district was found to be the area of maximum SCD gene frequency (9.02%), followed by Chandrapur (8.18%), Nagpur (4.0%), Amravati (3.73%), and Yeotmal (3.17%). The SCD was diagnosed from all tribal groups and 14 caste groups. Highest frequency of the disease was observed in *Gond* (14.28%) followed by *Pradhan* (11.49%), Bhil (11.42), *Teli* (10.48%), *Matang* (8.75%) and *Korku* (7.89%).[29]

A study assessed the prevalence of sickle cell disease among backward communities of Yavatmal District, Maharashtra using sickle cell solubility test to detect the presence of sickle haemoglobin and the positive samples were subjected to cellulose acetate membrane electrophoresis at pH 8.8 to confirm the diagnosis and classify Hb SS and Hb AS pattern. Out of 7568 screened population prevalence of sickle cell affected person was 21.41%. Electrophoresis pattern revealed 60.33% as heterozygous state Hb AS and 36.58% as homozygous state (Hb SS), 3.08% cases were found with other Hb variants.[30]

FIG 2 : DISTRICT-WISE PREVALENCE OF SICKLE CELL TRAIT IN MAHARASHTRA



The range of prevalence is 24 % - 4% and legend is not comparable to other states
Data is not available for the districts in grey

Figure 2 represents district-wise prevalence of sickle cell trait in Maharashtra as reported in a state-wide study.[25] Although, there are reports from missing districts on prevalence of Hb S, the data was not clubbed due to variance in methodology of conduct of the study.

Rajasthan: In Rajasthan, there are 228 communities that include 12 scheduled tribes which constitute 13.5% of the state's population. As per the census of the 2011, 5.73 million population are living in the scheduled area and 73.17% of them are tribal. *Bhil, Meena, Garasia* and *Damors* are the principal tribes residing in the areas.

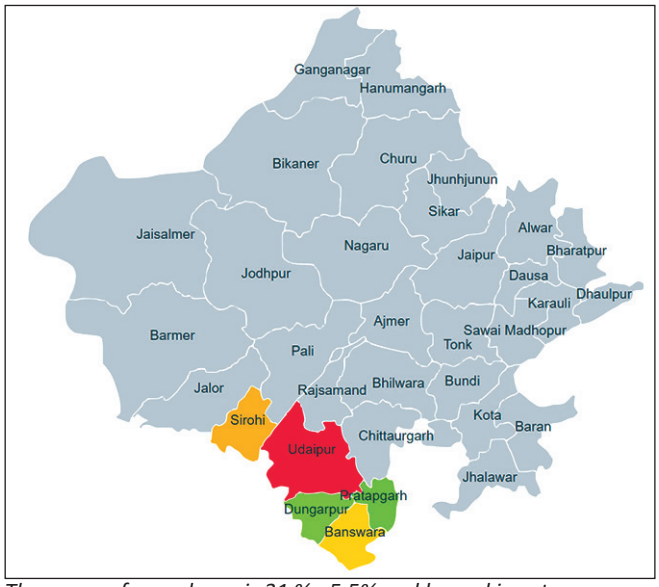
In scheduled area of Rajasthan, the maximum prevalence of Hb S variant gene was found to be 14.6% and 31.14% in *Gameti* and *Garasiya* tribes, respectively. [31] Subsequently, 0.6% to 7.35% incidence of sickle-cell gene in heterozygous (Hb-AS) was reported among different tribes of scheduled area ofUdaipur division. [32-36] From the tribal area of Rajasthan, 1.47% incidence of sickle-cell gene in homozygous state, Hb-SS (sickle-cell anaemia) in *Bhil* tribe has also been reported. [36] Besides the sickle cell genes, genes of other mutant Hb variants (Hb-D, E, C, J and H) have also been found in people of scheduled area of Rajasthan. This indicates that the state of Rajasthan is pool of diverse Hb variants. Therefore, more haematological studies are required to screen the people of different caste groups residing in desert and arid environments of Rajasthan for current status and evidence of endemicity of any new Hb variants.[37] Figure 3 represents the district-wise distribution of SCT in Rajasthan as reported in a review paper. [37]

A study was undertaken in the scheduled areas Pratapgarh, Banswara, Dungarpur, Udaipur (parts) and Abu Road block of Sirohi districts of Rajasthan to conduct sickle cell screening on the boarding students 6-12 years of age from the MaaBadi Centres. The prevalence of sickle cell disorder was reported as 5.8% in the tribal sub-plan districts of Rajasthan. Among the sickle cell disorder cases, the prevalence of the heterozygous was 5.61% and homozygous prevalence was 0.17%. The prevalence of the sickle cell disorders was 10.5% in the Sirohi district, which was highest among all the districts. This was followed by Banswara (7.42%) and

Udaipur (6.53%). The prevalence of sickle cell disorder in Dungarpur and Pratapgarh districts were 1.89% and 5.51% respectively. The highest prevalence of sickle cell disorder was reported in the Garasia tribe and the prevalence was 13.81%.[38]

During May 2014-December 2015, health checkup camps for tribal children was organized in Sirohi and Udaipur districts of Rajasthan for tribal (*Garasia*) children under the age of 15 years. A total of 1090 children were screened. The prevalence of sickle cell disease among tribal (*Garasia*) children of Sirohi and Udaipur districts was found to be 8.53% of which 0.77% were homozygous (Hb SS), whereas 7.7% were heterozygous (Sickle Trait/HbAS).[39]

FIGURE 3: DISTRICT-WISE PREVALENCE OF SICKLE CELL TRAIT IN RAJASTHAN

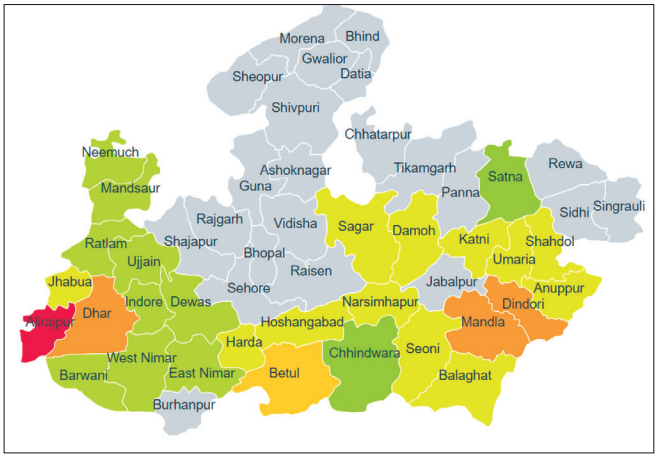


The range of prevalence is 31 % - 5.5% and legend is not comparable to other states
Data not available for the districts in grey

CENTRAL INDIA

Madhya Pradesh: Madhya Pradesh State contributes to about 15.0% of the total tribal populations of India, and tribal communities have been reported to suffer from various haemoglobinopathies. Madhya Pradesh has the highest load with an estimated number of 9,61,492 sickle heterozygotes and 67,861 sickle homozygotes. In addition, 27 of the 45 districts of Madhya Pradesh fall into the sickle cell zone, and the pervasiveness of sickle haemoglobin (HbS) fluctuates between 10% and 33%. Four tribal districts of the state namely Alirajpur, Anuppur, Chhindwara, and Dindori constitute around 75% of the existing cases of sickle cell anaemia according to the annual report 2020–2021.[40] Figure 4 presents the prevalence and district-wise distribution of sickle cell trait in the state of Madhya Pradesh.[41]

FIG 4 : DISTRICT-WISE PREVALENCE OF SICKLE CELL TRAIT IN MADHYA PRADESH



The range of prevalence is 25% - 10%and legend is not comparable to other states
Data not available for the districts in grey

A recent study screened a total of 3992 tribal individuals comprising students of Tribal schools, ashrams of Dindori, Mandla, and Chhindwara districts of Madhya Pradesh State. In this study, prevalence of homozygous sickle cell disease (0.7%), sickle cell trait (14.4%), b-thalassaemia trait (1.4%) was observed. The prevalence of sickle cell trait varies from 5.9 to 34.7%. The allele frequency of sickle cell gene was highest in the *Pradhan* tribe followed by the *Panika* tribe. Dindori district had the highest prevalence of sickle cell

trait. The *Gond* tribe is the major tribe of Madhya Pradesh with the prevalence of homozygous sickle cell disease in the range of 6.0 to 33.0%, whereas in the *Baiga* tribe, it varies from 6.0 to 20.0%.[42]

Similarly previous studies also reported the uneven distribution of prevalence of sickle cell trait among different-tribes.[43-47]

Chhattisgarh: 32% of population is of tribal origin in Chhattisgarh State and as public health measure they have started a screening programme for sickle haemoglobin which focuses on children aged 3–15 years since 2007. This programme had two objectives, the detection of patients with an SS phenotype who are referred for clinical care, and the education and counselling of subjects with the sickle cell trait in order to reduce the number of births affected by sickle cell disease. Target population selected for screening was aged 3–15 years and was approached in schools at village level. Screening was initially performed by solubility tests on fingerprick samples in the field and those with positive tests have venepunctures for haemoglobin electrophoresis. In this programme, 17,18,909 individuals from 11 districts and special camps in six districts were screened for presence of sickle cell anaemia. These 17 districts include Raipur, Baloda Bazar, Gariyaband, Dhamtari, Mahasamund, Durg, Balod, Kabeerdham, Bemetara, Kanker, Kondagaon, Mungeli, Raigarh, Dantewara, Korba, Bilaspur, Bastar and Narayanpur. The average prevalence for sickle cell carrier/trait (HbAS) was 11.71%, whereas it was 0.46 % for sickle cell disease. In this study, the highest occurrence of sickle gene was observed in *Gond* (20.63%), followed by *Halbi* (10.40%), *Khadiya* (5.03%), *Sanwra* (3.78%) and *Uranmi* (3.27%) tribes. In non-tribals groups, the highest occurrence was depicted by *Teli* (13.1%) followed by *Panika* (5.48%), *Agharia* (5.08%) and *Rawat* (4.97%) in OBC while in the SC category, *Satnami* (6.21%), *Ganda* (5.70%), *Mahar* (4.97%) and *Gharsiya* (1.46%). SCA was also seen among the general social group with a highest prevalence in *Brahmin* (0.1%) and *Rajput* (0.08%) communities.[48-50]

A study assessed the prevalence of SCD among school-age children (3–15 years age) in different regions and social categories of population of Chhattisgarh using the data generated through SCD screening programme in Chhattisgarh. The calculated prevalence of carrier state (AS) in ST, SC, OBC and GEN categories was found to be 9.56, 8.33, 10.82 and 6.30%, respectively. Similarly, the calculated prevalence of sickle cell disease (SS) in ST, SC, OBC and GEN categories was found to be 0.35, 0.31, 0.42 and 0.26%, respectively by the researchers.[51]

A pilot study from Raipur in Chhattisgarh, was undertaken where 1158 neonates were screened and 5.2% were sickle heterozygous, five babies had sickle cell anaemia and one had sickle-β-thalassaemia.[52]

A study was undertaken to assess the association between sickle cell anaemia (SCA) and glucose-6-phosphate dehydrogenase (G6PD) deficiency from *Sahu* and *Kurmi* population of Durg and Rajnandgaon district of Chhattisgarh. Among 982 samples collected from Durg, 9.26% were found sickle positive and out of 767 samples from Rajnandgaon, 6.77% were found sickle positive and 106 individuals were found G6PD deficient among which 66 were sickle positive.[53-54]

NORTHERN INDIA

Uttarakhand: Tribes of Uttarakhand mainly comprise five major groups - the *Jaunsari* tribe, *Tharu* tribe, *Raji* tribe, *Buksa* tribe, and *Bhotiyas*. In terms of population, the *Jaunsari* tribe is the most significant tribal group of the state.A survey collected data from various Primary Health Centre's, Certified Pathology labs and district hospitals of Kumaun Region and analyzed the status of anaemia, thalassemia trait and variants, sickle cell β thalassaemia and thalassaemia major in the state. It was reported that that most of the cases of haemoglobinopathies including Hb S are present in Udham Singh Nagar, followed by Nainital, Pithoragarh, Almora, Champawat, and Bageshwar. Although, most of the cases were thalassaemics but presence of sickle cell disease and trait was also noted. Sickle cell diseases are very common in tribal communities, especially prevalent in *Tharu* communities in Sitarganj area.[55] Similar results were reported by a three-year study conducted in health care facility of Uttarakhand.[55]

Uttar Pradesh: Uttar Pradesh is not known to be prevalent with HbS. However, an institution-based study conducted between 2009 and 2012 among pre-marital candidates, pregnant mother with known suspicious or unknown family history, clinically suspicious or haemoglobin fall patients referred by the physician and some self participants assessed the prevalence of haemoglobinopathies in north UP. The study reported haemoglobinopathies among the participants 12.01%, with β- thalassaemia heterozygous individuals (5.04%) was the most frequently encountered quantitative haemoglobinopathies, followed by HbAE (3.32%), β-thalassaemia homozygous state (0.43%), HbE β-thalassaemia trait (1.82%), HbAS (0.86%) and HbS β-thalassaemia trait (0.54%).[56]

EAST INDIA

Odisha: The state of Orissa is inhabited by 36.7 million of population,comprising 22.4% scheduled tribes and 16.2% scheduled caste people. HbS variant haemoglobin is known to be prevalent in the tribal areas of Odisha, however there is paucity of population-based screening studies in literature.[1]

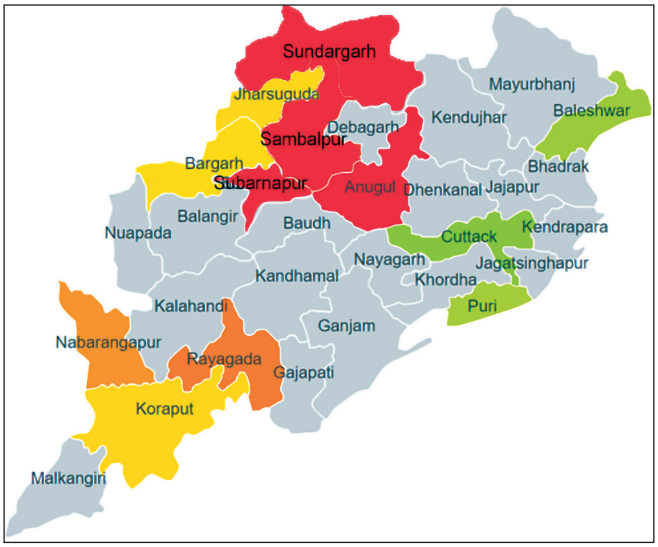
A cross-section of 15 major tribal communities from different parts of Odisha was randomly screened for haemoglobin variants and G6PD deficiency. High frequencies of sickle cell haemoglobinopathy (0-22.4%) and G6PD deficiency (4.3 to 17.4%) were found with 12 individuals inheriting both these abnormalities.[54] Unpublished data from Odisha Sickle Cell & Thalassaemia Control Programme involving 11 districts of the state covering 61,409 ante-natal women suggests 9% prevalence of SCT while 0.3% and 4.3% for SCD and beta thalassaemia respectively. Figure 5 presents the data on prevalence of SCT from the programme.[57]

In the Kalahandi district in Odisha, 1668 newborns were screened and 19.03% of tribals were sickle heterozygous and 2.1% with homozygous sickle cell disease were identified.[58]

A cross-sectional study for sickle cell carrier screening was conducted in Koraput district of Odisha. A total of 1092 individuals from 22 villages were screened for sickle cell trait. Out of 1092 individuals, 9.43% individuals were found to be sickle cell carriers. Also, the study found a significantly higher prevalence of sickle cell haemoglobins among SCs (9.98%) than STs (3.33%).[59]

An observational study was carried out for a period of 2 years at multiple institutes among the blood samples (cases) advised for diagnosis of different haemoglobin disorders. The most common abnormal haemoglobin disorder was found to be sickle haemoglobin variant (48.67%) which was diagnosed as sickle cell trait (22.1%), homozygous sickle cell anaemia (20%), double heterozygous state of sickle cell-b-thalassaemia (3.2%). The second prevalent variant was b-thalassaemia states (11.32%) which was diagnosed as b-thalassaemia trait, b-thalassaemia major, and double heterozygous state with sickle cell, haemoglobin E and haemoglobin Lepore.[60]

FIG 5: DISTRICT-WISE PREVALENCE OF SICKLE CELL TRAIT IN ODISHA



The range of prevalence is 26 % - 7.4% and legend is not comparable to other state
Data not available for the districts in grey

26 should be 36

A study from Medical College, Cuttack assessed the spectrum and magnitude of hereditary haemoglobin disorder from a large sample size comprising those referredfor evaluation of anaemia from 2008 to 2017. A total of 21,371

patients were enrolled during these 10 years of study period. Out of which 50.2% cases were diagnosed with different types of haemoglobinopathies. Beta-thalassaemia was detected in 54.06%, HbS 52.48% and HbE in 9.19%. Other haemoglobinopathies like a-thalassaemia,HbD Punjab, Hb Lepore, HPFH were present in less than 1% each.[61]

Jharkhand: The predominant population of the newly formed state of Jharkhand, is tribal. Incidence of SCD is 3.3% in tribal children of Chotanagpur (Jharkhand) which is upto 10% in various parts of the state. [4] In a recent study on the prevalence of haemoglobinopathies in the eastern region of India (eastern Uttar Pradesh, western Bihar, Chhattisgarh and Jharkhand); it was reported that the frequencies of thalassaemia as well as HbS traits to be the same (3.6%), but while BTT was distributed uniformly through the region, HbS was confined to Chhattisgarh and Jharkhand, the regions abundant in tribal communities. However, in Jharkhand, which shares borders with Uttar Pradesh, Chhattisgarh, Odisha, Bihar and Bengal, HbS was seen in the populations adjacent to Chhattisgarh and Odisha but not in those bordering UP and Bengal.[62]

A report assessing the genetic basis of the discriminatory distribution of HbS in different regions of Jharkhandrecorded the number of HbS casesas 3.3%. The sub-categorisation of the tribal samples from Sahibganj and Tatanagar districts included communities of *Santhals, Patars and Oraon*. Though tribals constitute major part of the population, only 3% of the examined samples showed HbSas against 13% in Chhattisgarh, with a rather uneven region-wise distribution, it being highest in Tatanagar (10%), nil in Sahibganj and only a minor presence in Garhwa and Ranchi. However, this distribution follows a regional bias: Tatanagar is contiguous with the Odisha border whereas Sahibganj is adjacent to West Bengal. The other two regions, Garhwa, borders with UP and Chhattisgarh, while Ranchi, being the state capital, is nearly at the centre of Jharkhand state.[63]

West Bengal : A community based screening was conducted from June 2010 to August 2013 to evaluate the prevalence of β-thalassemia, HbS, HbD, HbE in the state. A total of 50,487 cases were subjected to study from different districts of rural areas of West Bengal by arranging camps in schools, colleges and university also for screening of individuals for detection of different haemoglobinopathies using HPLC. The prevalence of β-thalassaemia trait was 6.61% making this the major haemoglobinopathy in West Bengal, followed by HbE trait at a prevalence of 2.78% in the study population.A total of (0.56%) of sickle cell trait were detected in the study.[64]

Earlier studies by Mohanty *et al*. have shown a prevalence of 0.14% and 0.13% from Kolkata and Dibrugarh respectively.[65] A study from Kolkata done on retrospective data of a diagnostic centre showed only 0.276% of sickle cell trait amongst 14, 145 cases included in the study.(66) Another institution-based study from North Bengal included cases of pallor and weakness from camps and diagnosed Hb S variant with HPLC reported sickle cell haemoglobin variant in 2.16% of the study subjects.[67] Unpublished data from state screening revealed a prevalence of Hb S as 0.1% while that of thalassemia trait as nearly 10%.

SOUTHERN INDIA

Tamil Nadu: HbS haemoglobin was first described in the Nilgiri Hills of northern Tamil Nadu in 1952. The scheduled tribal population of Tamil Nadu was found to be 6.51 lakhs widely distributed in 30 districts constituting 36 tribes. The Nilgiri district includes six primitive tribal communities viz., *Todas, Kothas, Kurumbas, Irulas, Paniyas* and *Kattunaikkans* unevenly distributed in forest and hilly areas of six talukas of this district. The distribution of SCD in various tribal populations in Nilgiri district of Tamil Nadu has been studied to identify the high risk areas. Among these population 11.7% were found to be sickling homozygous (HbSS), whereas 28% population examined had heterozygous state (HbAS). The highest incidence of SCD cases were reported in six village panchayat namely Cherangode, Nellakota, Jakkanarai, Konakkarai, Kengarai and Arakkode. A maximum of cases were recorded in Jakkkanarai of Kotagiri taluka.[68]

The sickle cell gene is known to be wide spread among people of the Deccan plateau of central India with a small-

er focus in the north of Kerala and Tamil Nadu. Extensive studies performed by the Anthropological Survey of Indiahave documented the distribution and frequency of the sickle cell trait which reaches levels as high as 35% in some communities.[65]

Kerala: In Kerala, sickle cell anaemia is prevalent in Wayanad district and the Attappady block of Palakkad district. Prevalence of homozygous sickle cell disease among tribals in Wayanad is about 0.31% and that of sickle cell trait is about 4.33%.[69]

A population-based study of gene frequencies and disease characteristics using haemoglobin electrophoresis was done in 1016 subjects belonging to the tribal and Chetti communities in Wayanad district. The study was conducted in schools by evaluating everyone present at the time of the visit. The gene frequency of haemoglobin S ranged from 0.019 in Kattunayakan to 0.196 in Wayanadan Chettis.[70]

Andhra Pradesh and Telangana : Andhra Pradesh and Telangana are the Indian states with a total population of 76.2 million and harbour 5 million tribal population that constitutes 6.6% of the total population. These two states are rich reservoirs of HbS gene. The prevalence of carriers (Hb AS) is ranged up to 24.5% in Andhra Pradesh and 30% in Telangana. In an analysis of 13,922 people from 27 tribal communities conducted to estimate SCD from different studies among the states, it was found that Hb S gene was present in almost all tribal groups and the gene frequency ranged from 0.0014 (in *Chenchu* tribe) to 0.1545 (in *Pardhan* tribe). Based on Hb S gene frequencies, birth rate and inbreeding coefficient of these tribes, the expected births with SCD are calculated. The expected number of children born with SCD is 1.8 and 1.7 per 1000 births in Andhra Pradesh and Telangana states, respectively.[71]

In Andhra Pradesh, the highest frequency of sickle cell carriers are recorded among tribes, such as *Pardhan, Konda Kammara, Bod Mali, Manzai Mali, Valmiki, Parangi Poraja*, etc., which inhabit hilly terrains with dense forest cover. Interestingly members of the *Yanadi* and *Yerukula* tribes residing in the plain areas show total absence and very low incidence of sickle cell trait, respectively. Among early surveys, very low frequencies of homozygous sickle cell anaemic individuals were recorded in the state. Most of these studies were carried out as part of population variation investigations with anthropological perspective and hence all these studies are based on the screening of only adults. The sickle cell anaemic children with severe phenotype may have might have expired. The frequencies of sickle cell anaemia patients in the dense forests of Andhra Pradesh, varies between tribes such as *Pardhan* (31.78%), *Konda Kammara* (22.3%), *Bod Mali* (15%), *Valmiki* (14.8%), *Manzai Mali* (13,7%), etc.[72]

A study assessing prevalance of sickle cell anaemia among the *Thotis*, of Andhra Pradesh reported 12.84% individuals who had positive screen test for sickle cell haemoglobin, 9.32% were heterozygous (AS) for sickle cell trait while 2.52% were homozygous (SS).[73]

NORTH EAST INDIA

Assam : Haemoglobinopathy, particularly HbE and sickle cell haemoglobin (HbS) and thalassaemia are considered to be contributing factor in occurrence of anaemia in Assam and HbS was reported to be mostly restricted to the tea garden community of Assam. A community-based study conducted at 16 tea estates of Assam assessed the determinants of anaemia among adolescent girls . They reported that 12% of the anaemic girls had Hb S.[74] Another study carried out to determine the frequency and types of haemoglobinopathies in the tea garden community near Dibrugarh town assessed 250 cases from two different tea gardens, irrespective of age and sex. The study reported abnormal haemoglobins asHbE trait (1.6%), HbS trait (12.0%) and HbS disease (2.0%) among the study population.[75]

The study was carried out to determine the prevalence of haemoglobinopathies and β-thalassaemia among the tea garden workers of Assam, where 1204 samples were assessed with HPLC. The study results indicated a higher prevalence of β-thalassaemia (3.07%) among the *Munda* ethnic group and higher prevalence of sickle cell anaemia (4.73%) among the *Lohar* ethnic group. 1.66% of the participants were compound heterozygotes of β-thalassaemia which

co-inherited with HbE and HbS.[76] A community-based cross-sectional study conducted among 770 numbers of adult females belonging to the tea garden community reported momozygous Hb SS in 2.4% and heterozygous Hb AS among 14.2% of study population.[77]

Tripura: Nineteen tribes are represented in the population of Tripura, the two largest being the *Tripuri* and *Reang*, which together accounted for 71% of the tribal population in 2001. Newborn screening for haemoglobinopathies was also undertaken in the malaria endemic region in Agartala in Tripura where HbE is widely prevalent but HbS is also seen among the tea garden workers who are migrant laborers from other states.[78]

In summary the data is useful as it sheds light on the magnitude of the problem, but the varied target populations, different test methodology used and other lacuna, limit the use of this data for good policy implementation. Registry data and well-planned screening from the 16 states, particularly from the districts with high sickle cell burden have been initiated and this complete dataset will be invaluable for improving the care that the patients receive.

SUMMARY:

1. Exact prevalence of SCD in most parts of India based on population based survey is not available.
2. Sickle Cell Disease (HbAS, HbSS, Sickle Beta-Thal) have variable frequency of 1 to 44%, constitute one major public health problem. It varies from place to place.
3. SCD is considered a major socio-economic burden of India by considering its magnitude and multiple impacts.

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CHAPTER 2

Screening And Diagnosis

The objective of this section of the ICH guideline is to outline the laboratory investigations and tests available for diagnosis and screening for sickle cell disease (including HbSS, HbS/β0or HbS/β+thalassemia, HbSE, HbSD-Punjab and HbSC diseases, etc.) as well as the carrier state. It aims to provide laboratory and clinical haematologists with an evidence-based background to scientifically select the most appropriate and feasible laboratory test option(s) in various Indian practice settings. Important considerations in test performance and interpretation are included where relevant.

Evidence-based recommendations are provided wherever possible. For several issues, however, only expert guidance is given and these are clearly indicated as such. Test selection, performance and reporting depend heavily on, and must always be tailored to the clinical setting and scenario (population or hospital-based screening, anaemia/thrombosis work-up, prenatal diagnosis etc.). Readers must therefore always take the same into account while applying this guideline. Test procedures are not provided in this guideline for brevity.

DEFINITIONS AND TERMINOLOGIES

Some key terminologies pertinent to disease nomenclature and laboratory testing are defined in **Table 1:**

TABLE 1 - DEFINITIONS AND TERMINOLOGIES PERTAINING TO THE SICKLE CELL HAEMOGLOBINOPATHY. ENTITIES ARE ARRANGED IN ALPHABETICAL ORDER.[1–7]

TERMINOLOGY	DEFINITION
Adult haemoglobin (HbA)	The predominant normal haemoglobin fraction. It surpasses fetal haemoglobin as the major haemoglobin fraction by 6 months of age; levels of over 90% are attained by 1-year of post-natal life and subsequently maintained at 92-96% throughout life. Structurally, HbA comprises of two α-globin and two β-globin polypeptide chains and is denoted as α2β2.
Amplification-refractory mutation system (ARMS) PCR	A modified conventional PCR technique to detect single base-pair changes by using sets of allele-specific or sequence-specific primers for selective DNA amplification. Commonly used to detect point mutations in the β-globin gene.
Direct DNA sequencing	A technique to determine the linear nucleotide sequence of an amplified DNA fragment (usually up to 1000-1200 base pairs in length). It is most often based on the termination of elongating DNA chains by a fluorescently-labelled dideoxynucleotide (Sanger method) followed by automated ultra-high-resolution capillary electrophoresis.
Fetal haemoglobin (HbF)	A normal haemoglobin fraction that constitutes the predominant form of haemoglobin for oxygen carriage during fetal life. It reduces by one-year after birth to levels of approximately 1-1.5%. Structurally, HbF comprises of two α-globin and two γ-globin chains and is denoted α2γ2.
Gap-PCR	A specific PCR-based technique to detect large deletional mutations using primers flanking the deleted regions. It is primarily used to detect deletions in α- or δβ-thalassemia, HPFH and Hb-Lepore rearrangements. Since the normal result is generation of no amplified product, internal controls are especially important in this PCR-type. A multiplexed gap-PCR is available to simultaneously detect eight α-thalassemia deletions that are commoner in India.
Haplotype	A set of polymorphic genetic markers that are located spatially close to each other on the genome, and are hence likely to be co-inherited together over generations. In the context of the sickle cell mutation, it refers to the coinherited milieu of the β-globin gene cluster, including the gamma globin genes, β-locus control region and other regulatory loci that introduce variation in fetal haemoglobin levels between sickle cell disease patients in various ethnic groups, and thus affect disease expression.
Haemoglobin A2	A minor normal haemoglobin fraction comprising 2.0-3.3% of adult haemoglobin and composed structurally of two α-globin and two δ-globin chains (α2δ2).

TERMINOLOGY	DEFINITION
Haemoglobin capillary zone electrophoresis (CZE)	A high-throughput, fully-automatable technique for rapid and high-resolution separation of haemoglobin fractions by electrophoresis in silica-coated capillaries subjected to high voltage currents. Charged molecules are separated by their electrophoretic mobility at a specific pH in an alkaline buffer. Separation occurs according to the electrolyte pH and electro-osmotic flow. CE has a steady flow result in narrower peaks and better resolution. It has emerged as a viable alternative to CE-HPLC for screening of thalassemias and haemoglobinopathies in modern hematology laboratories.
Haemoglobin D-Punjab (HbD-Punjab)	Also known as HbD-Los Angeles, this β-globin chain structural variant results from an amino acid substitution (glutamic acid to glycine) in exon 3 (HBB:c.364G>C p.Glu122Gln). Common in north-western India, HbD-Punjab is nearly asymptomatic in heterozygous, homozygous and in a compound heterozygous state with β-thalassemia. It however interacts with HbS to give rise to moderately severe hemolytic anaemia with vaso-occlusive crises.
Haemoglobin E (HbE)	A β-globin chain structural haemoglobin variant with additional thalassemic features. It results from an amino acid substitution (glutamic acid to lysine) at position 26 (HBB:c.79G>A p.Glu27Lys) leading to the creation of an alternative splice site, and leading to reduction in β-globin chain (β^E) output to ~25-30% of normal in heterozygotes. HbE is the commonest haemoglobin variant in eastern India and southeast Asia.
Haemoglobin electrophoresis	A technique to separate haemoglobin variant/s based on their net electrical charge. It uses alkaline (cellulose acetate; pH 8.4-8.6) or acidic (citrate agar; pH 6.0) gels or membranes in conjunction with buffer-filled tanks to maintain an electrical gradient. Both manual and automated versions are available.
Haemoglobin S / sickle cell haemoglobin (HbS)	The commonest and the most well-studied of all human structural haemoglobin variants, HbS occurs due to single amino acid substitution (glutamic acid to valine) at position 6 of the β-globin chain (HBB:c.20A>T p.Glu7Val). Its deoxy form tends to polymerize and precipitate, resulting in characteristic sickle-shaped RBCs.
Haemoglobinopathies	A group of blood disorders characterized by structural (qualitative) defects in one or more of the globin chains, giving rise to a variant haemoglobin with altered physiochemical properties.
Hereditary persistence of fetal haemoglobin (HPFH)	Relatively benign/asymptomatic haemoglobin disorders/variations resulting in an increase in HbF levels post-infancy. HPFH are extremely heterogeneous genetically, arising due to either large deletions in β-globin gene cluster (deletional HPFH), point mutations in promoters of γ^Aor γ^G globin genes (non-deletional HPFH), or due to one or more of several trans-acting genetic events.
Cation-exchange high-performance liquid chromatography (CE-HPLC)	A quantitative technique to separate RBC lysates into haemoglobin fractions (HbA0, HbA2, HbF and variants) depending upon their elution time windows utilizing cation-exchange columns. This rapid, high throughput and mostly fully-automated technology is often used as the first-line screening technique for thalassemias and haemoglobinopathies in a non-resource-constrained setting.
Multiplex ligation-dependent probe amplification (MLPA)	A modified multiplex-PCR followed by capillary electrophoresis-based fragment analysis technique that detects copy number changes (1000-100,000 bp) across multiple target regions using a single primer pair and multiplexed target-specific probes. Useful to detect large deletions and determining breakpoints in α- and β-thalassemia.
Next-generation sequencing (NGS)	A high-throughput massively parallel method of sequencing large DNA/RNA segments at high fidelity. This may be applied to targeted regions, exomes or the entire genome. Globin genes, due to their relatively small sizes, do not usually require NGS for diagnostic evaluation. Exceptions however abound, in the form of hyperunstable variants missed by CE-HPLC/CZE, detection of low frequency fetal alleles in NIPT/NIPD, etc.
Non-invasive Prenatal Testing or Diagnosis (NIPT or NIPD)	Techniques for analysis of cell-free fetal DNA (or less commonly, fetal cells) from maternal blood specimens. This may be used to screen for common chromosomal conditions / aneuploidies (NIPT) or specifically test for a known parental/familial disorder (NIPD).

TERMINOLOGY	DEFINITION
Reverse dot-blot hybridization assay	A rapid DNA-based test for mutations/polymorphisms by using immobilised targeted oligonucleotide probes. Common variants and β-thalassemia point mutations prevalent in specific locales can be screened using this relatively simple technique.
Sickle cell anaemia	Homozygous (SS) state for the sickle cell mutation, wherein both the copies of the β-globin gene (HBB) on chromosome 11 carry the c.20C>T mutation, and no normal β-globin chain is synthesized.
Sickle cell disease	An umbrella term that includes all symptomatic individuals possessing the sickle cell variant at the β-globin gene locus. It includes sickle cell anaemia (SS state), sickle-β-thalassemia, sickle-haemoglobin D-Punjab, sickle-haemoglobin E and other states. Sickle cell trait i.e. heterozygotes are typically excluded from this rubric. A few publications expand SCD as sickle cell disorders, and they include sickle cell traits as well. Hence, use of the unqualified acronym SCD should be avoided.
Sickle cell trait	The heterozygous state for the sickle cell mutation wherein an individual possesses one β-globin gene with the sickle cell mutation, while the other β-globin gene is normal. Also referred to as the carrier state for sickle haemoglobin.
Thalassemia	An autosomal recessive quantitative globin gene defect resulting in reduced or absent synthesis of one or more of the normal globin chains. They are named after the specific globin gene(s) that are affected, and superscript notations of 0, + and ++ are affixed to denote the degree of reduction in chain synthesis (for e.g., β^0, β^+, β^{++}).
Thalassemic haemoglobinopathies	Distinct subtypes of haemoglobinopathies in which the structural defect in the normal globin gene also results in reduced quantitative output of the chain. Examples include haemoglobins E, Lepore, Constant Spring and Koya Dora.

COMMON INDICATIONS FOR DIAGNOSTIC LABORATORY TESTING FOR A SICKLE CELL DISORDER [3,7–11]

- Work-up of a patient suspected to have a sickling disorder: Typical presentations include consequences of:
- vascular occlusion and ischemic necrosis (avascular necrosis of bones leading to dactylitis/hand-foot syndrome/ shortened digits and osteomyelitis, acute splenic sequestration, initial chronic hypersplenism followed by autosplenectomy and hyposplenism, cerebral haemorrhage and infarcts, lung infarcts leading to fibrosis, heart failure and infections, retinopathy, priapism, renal papillary necrosis etc.), or.
- hemolysis (anaemia, jaundice, gallstones etc.), or.
- both hemolysis+vascular occlusion (for e.g., leg ulcers, renal dysfunction, pulmonary hypertension etc.) [7,10,11]
- Family screening of relatives of a patient known to have a sickling disorder.
- Screening of populations at higher risk of inheriting the disease (for e.g., tribal populations, certain central Indian states.) [12–15]
- Screening of populations where interventions will be desirable for disease control, prevention or timely management (for e.g., pregnant women, couples coming for pre-conceptional counselling, college students, other younger adults of marriageable age, neonates.[16–18]
- Confirmation of an incidentally detected variant peak on CE-HPLC and Capillary Electrophoresis done for HbA1c quantitation in diabetes mellitus testing.[19]
- Screening of specific target populations at higher risk of developing disease complications (for e.g., in areas with high prevalence of the sickle cell gene, one could consider screening prior to elective surgeries in high-risk areas, before posting personnel to high altitude locations, participants in high-intensity sports etc.) [20–24]

TARGET POPULATIONS FOR SCREENING FOR SICKLE CELL HAEMOGLOBIN (HBS) [12–18,20–22,24]

In the absence of symptoms, screening tests may be done in tribal populations, antenatal women (ideally in the first trimester, but also those presenting later in pregnancy), school and college students and newborn babies. Husbands, wives

and fiancées as well as siblings of all those detected to carry a significant haemoglobinopathy or thalassemia must also be screened. Testing of extended family members must be encouraged.

Screened persons may also include mountaineers, travellers, armed forces personnel posted to high altitudes, sportspersons, or other groups at risk for exertional /heat-related injuries etc. as per governmental/organizational/employers' policies.

LABORATORY IDENTIFICATION OF SICKLE CELL HAEMOGLOBIN (HBS)

Haemoglobin S can be readily detected at the protein and the molecular level by a variety of tests with varying degrees of specificity and sensitivity.[4,5,7] These can be broadly classified into screening and diagnostic tests, although one category may also serve as another, depending on the laboratory setting.

SCREENING TESTS

These technically simpler and lower cost tests have been applied for larger scale screening of general or specific populations. They aim at high sensitivity, typically sufficient to detect even heterozygotes and should be interpretable by trained non-medical staff. Additional advantageous characteristics would be non-dependence on electric supplies, not being affected by high ambient temperatures or requiring air conditioning or refrigeration.[4,5,7]

All screen-detected cases of sickle cell disorders need to be subsequently confirmed by a diagnostic test using an independent technology.[4,5,25]

THE COMMONLY EMPLOYED SCREENING TESTS ARE

1. ***Sickle solubility test:*** This inexpensive test requires commonly available reagents and glassware along with a standard centrifuge. It is also available from multiple manufacturers in the form of kits that can be stored at room temperature, with pre-prepared reagents.The sickle solubility test is based on the principle that on exposure to a concentrated phosphate buffered solution containing sodium metabisulfite or dithionite and a red cell lyzing agent, haemoglobin S from lysed erythrocytes crystallizes and precipitates, leading to turbidity in the solution. The interpretation is based on a visual inspection of the test tube and is enhanced by centrifugation, which is now a standard step in all procedures.

The test has sufficient sensitivity to detect HbS levels greater than 10%, making it suitable for use in virtually every setting (including mass screening) except for newborn screening.[4,5,7,25–29] The percentage of HbS in heterozygotes is approximately 40%, but declines with concomitant iron deficiency, megaloblastic anaemia or with co-inherited α-thalassemia to levels as low as 15-20%.[30–33] However, this test will not distinguish homozygous from heterozygous cases.

The newer generation of Sickle Solubility Test based on filter paper Eg. Watman Filter Paper with SICKLEVUE reagent is a very simple, user friendly and sensitive screening method with a lot of advantages especially at field.

2. ***Wet mount slide-based microscopic test for sickling:*** This test relies on incubating a minute volume of RBCs in an airtight cover-slipped suspension of 2% freshly prepared sodium metabisulfite or dithionite solution on a glass slide at 37 degrees Celsius and periodically examining it microscopically for the presence of typical crescent-shaped sickle cells. It is very important to let the preparation stand for 24 hours before declaring the test negative. However, this test will not distinguish homozygous from heterozygous cases.

Inexpensive, rapid, and sensitive, this test, however, requires a microscope, incubator and sufficient expertise or training to evaluate slides, making it cumbersome to use for screening large numbers of samples. In a routine hematology laboratory, it, however, can serve as a near-optimal confirmatory test for a sickle cell disorder discovered on HPLC/CZE/electrophoresis, due to its very high specificity via visualization of the sickled erythrocytes.[25,27,29,34,35] This is especially helpful as some non-S variant haemoglobins like HbM-Iwate and HbQ-Thailand can elute in the S-window on CE-HPLC as well as migrate in the S/D/G region on alkaline

pH electrophoresis.[34,36]

3. ***Haemoglobin electrophoresis at alkaline pH:*** Although technically more challenging, the cellulose acetate or paper strip electrophoresis at ph 8.4-8.6 have been used on a mass-scale to screen for the typical slow-migrating band. Other variant haemoglobins migrating with HbS are HbD-Punjab, HbD-Iran, HbG, Hb Lepore and HbQ-India. A further acidic pH electrophoresis is sometimes performed to distinguish HbS from HbD variants, however, practically the solubility or slide-based sickling tests are more feasible and equally confirmatory. Electrophoretic bands can be quantitated densitometrically, but the values show a high coefficient of variation for the smaller fractions.[4,5,7,25,37–40]
4. ***Point-of-care rapid tests (PoCRT):*** Several PoCRT devices have been developed for sickle cell disorders. These promising tests are based on diverse diagnostic principles. One technology involves different mobilities of cells with sickle and adult haemoglobin on filter paper after mixing with sickling-inducing reagents.[41–43] It has been successfully applied to neonatal screening, with 100% sensitivity and 83% specificity.[44]

Other applications use differences in erythrocyte density observed in multiphase aqueous systems, and antibody capture-based immunoassays.[45,46] Among the latter, the HemoTypeSC assay based on monoclonal antibody-based distinction of adult haemoglobin versus haemoglobin S and C by a competitive enzyme-linked, immunochromatographic lateral-flow assay has shown 100% accuracy in correct identifying the variant Hb, regardless of the haemoglobin F levels.[47] Another point-of-care immunoassay, SickleSCAN (BioMedomics™), rapidly distinguishes haemoglobins S, C andhaemoglobins other than S or C (most often, haemoglobin A) in dried blood spots with 100% sensitivity in infants 9 months or older.[48,49] Both the immunological assays require minuscule quantities (5-15 µl) of blood, are not interfered with by haemoglobin F and require no power source or instrumentation (droppers and tubes are included in the kit).[46,49]

Cellulose acetate paper-based microfluidic electrophoretic techniques like HemeChip with integrated stainless-steel electrodes (both quantitative and qualitative) require a power source.[50] One such micro-engineered device, Gazelle™, tested in 960 Indian patients, demonstrated over 99% sensitivity and specificity to distinguish sickle cell disorders from normal, as well as distinguish heterozygotes from those more severely afflicted.[51]

NOTE: Automated analyzer derived red blood cell indices or the peripheral blood features are not sufficiently sensitive to serve as reliable screening tests for the sickle cell disorders.[7,25,52,53] They may however, be of diagnostic help in distinguishing sickle cell anaemia (SS) from compound heterozygous sickle-β-thalassemia state.[54] Even in the latter scenario, it is important to remember that sickle cell anaemia (SS state) can display microcytic hypochromic red cell indices in the presence of iron deficiency or co-inherited α-thalassemia.[30–32,55] Table 2 lists more details on utility of peripheral blood features of sickle cell disorders.

DEFINITIVE DIAGNOSTIC TESTS FOR DEMONSTRATING HAEMOGLOBIN FRACTIONS

These are confirmatory tests for not only sickle cell diseases but for all hemogobinopathies and thalassemia.

They include tests based on highly-specific and fully automatable protein separation techniques including cation-exchange high-performance liquid chromatography (CE-HPLC) and high-voltage capillary zone electrophoresis (CZE). Isoelectric focussing and capillary isoelectric focussing are less commonly used.

1. ***High-performance liquid chromatography (CE-HPLC):*** This is based on the principle that positively-charged haemoglobin molecules adsorb onto a negatively-charged stationary phase in a microbore precision column till they are eluted out into a high-precision gradient-generating liquid buffer (mobile phase). The duration of adsorption is termed "retention time" and once the flow rate, temperature and pressure have been standardized, this time is precisely aligned to the chromatographic affinities of specific haemoglobin molecules, permitting their identification.[4,5,7,35,56,57]

Currently one of the leading technologies for haemoglobinopathy diagnosis due to its speed, precision, labour-saving nature, low sample requirement and versatility (it diagnoses both thalassemia and haemoglobinopathies and quantitates HbA1c), CE-HPLC is nonetheless capital-intensive and re-

quires expertise to run and report.[4,5,7,56]

2. ***Automated capillary zone electrophoresis:*** Performed in glass capillaries, this technique relies upon ionic migration in an alkaline buffer with electro-osmotic flow to segregate the different haemoglobins, whose identity is then determined as per their zone of separation in comparison to adult haemoglobin. High-end instruments have higher throughput than comparable CE-HPLCs, sample requirement is similarly low, and the results require pathologist-level interpretation.[4,5,7,56] Post-translational modified fractions of adult and variant haemoglobins are not separated from HbA, making interpretation more straightforward.[58] Unlike CE-HPLC, CZE can separate haemoglobin A2 from E and Lepore, and can also pick up minute quantities of haemoglobin Constant Spring, HbH and Hb Bart's.[7,37,59–62]
3. ***Isoelectric focussing:*** Utilization of an agarose, polyacrylamide, or cellulose acetate gel/plate with a pH gradient across the gel results in high resolution separation of haemoglobin fractions that migrate along the gel till they reach an isoelectric pH (i.e., have a net charge of zero) and immobilize. Despite its very resolution, densitometric quantification is difficult for low percentage but critical fractions (HbA2), and interpretation requires skill and experience.[7,60,61,63]
4. ***Other diagnostic techniques*** used in literature include liquid chromatography-mass spectrometry [64,65], image or photoacoustic flow cytometry [66,67], a variety of biosensors [surface plasmon resonance-based [68] or electrochemical genosensors [69], and optical tweezer-based red cell capture and analysis.[25,70,71] With several reported advantages, although they are yet to make the transition to routine diagnostics, they may do so in the future. Many of these are also being developed for point-of-care applications.

Number of tests required for a definitive diagnosis: Regardless of the initial screening of diagnostic technique applied, the detection of sickle cell haemoglobin (and, in fact, any variant haemoglobin) by any one technique remains presumptive until its identity is verified through a second technique based on an independent principle.[4,5,7,63] In this regard, the second technique, specifically for a suspected sickle haemoglobin in a microscope-equipped laboratory should preferably be the slide-based test for sickling, as it provides highly specific visual confirmation of the sickling phenomenon.[29,34]

RBC transfusions interfere with all techniques that quantitate haemoglobin fractions, and reduce the sensitivity of qualitative techniques. A history of recent blood transfusions must be sought wherever possible. A recent transfusion is not a reason to decline to test the patient, but the report must mention that values will be erroneous and that quantitative defects like thalassemia may be missed in transfused patients.

TABLE 2. AN OVERVIEW OF COMMON/WIDELY USED TESTS FOR THE DETECTION OF SICKLE CELL DISORDERS

TEST NAME	ACCURACY INDICES	ADVANTAGES	LIMITATIONS / PITFALLS	ROLE IN TESTING
Presence of sickled RBCs and other features on microscopic examination of a blood smear [7,52,53,72,73]	Sickled cells are generally not seen in smears from heterozygotes. In SS and Sβ-thalassemia, sickled cells vary from a few to 30-40%. Numbers tend to increase in times of crises. Sensitivity in SS is approx. 75% and specificity near-100%.	Low cost, easy availability. Apart from sickled RBCs, smears are useful to assess other lineages – for e.g., pancytopenia is seen in marrow infarction and in megaloblastic crisis (latter also shows macroovalocytes and hypersegmented neutrophils), hyperhaemolytic transfusion reactions (nucleated RBCs, spherocytes), stigmata of infections (toxic changes, maturational left shift, neutrophilia) or of hyposplenism (Howell Jolly bodies, thrombocytosis, target cells, erythroblasts, etc). Microcytosis is seen in Sβ-thalassemia and in iron deficient SS or those with co-inherited α-thalassemia.	Low sensitivity. Artifacts can mimic sickled cells.	Useful general test. Not suitable for primary diagnosis. Presence of circulating sickled appearing RBCs should prompt specific testing.
Sickle solubility test [26–29,74,75]	Positive when HbS is over 10% of total Hb. Accuracy varies widely between reports: sensitivity / specificity were 93.8% / 100% in a large Indian study, but only 45% / 90% in a Ugandan study and 88.9% / 79.4% in a report from New York.	Simple, low cost, rapid, requires low sample volume.	Cannot distinguish heterozygotes from homozygotes or compound heterozygotes. False negative in newborns, very low Hb (hematocrit should be corrected to ~0.50), coinherited α-thalassemia. Interferences (false positives) by leukocytosis, paraproteins, hyperlipidemia, erythroblastosis, RBCs with Heinz bodies.	Useful and convenient mass screening test (may be supplanted by point-of-care testing in the future). Positive tests should always be followed by definitive testing. Negative tests in clinically significant scenarios should also be reconfirmed by another technique.
Wet-mount slide-based microscopic test for sickling [29,34,57]	Detects HbS when it is around 10-20% or above as a fraction of total Hb. Sensitivity was 65% when evaluated at 15 minutes (would have been higher at extended incubations) and specificity 95.6% in a Ugandan study that declared it as more reliable, cheap and easy to perform vis-à-vis solubility test.	Highly specific, offers microscopic confirmation. Low cost, technically simple.	Requires basic microscopy skills. Sickle cell traits may take up to a few hours to show sickled RBCs. Incorrect procedure, esp. careless reagent preparation can lead to false negative results.	Most useful as a rapid confirmatory test for HPLC/CE detected S-peak.

TEST NAME	ACCURACY INDICES	ADVANTAGES	LIMITATIONS / PITFALLS	ROLE IN TESTING
Haemoglobin CE-HPLC [4,5,7,35,56,57]	Peaks as low as 1-2% eluting in the S-window are identified.	Extremely sensitive, rapid, low sample volume, backed-up by a large body of literature, fully automatable, high throughput. β-thalassemia, HbH and variants detected in one procedure. Post-translationally modified adult haemoglobin detection enables incidental detection of diabetes mellitus, corroborates hemolysis (low P2%).	Capital intensive. Requires trained manpower and expertise. False elevation of HbS due to post-translational modified adult haemoglobin (for e.g., carbamylated forms). Second confirmatory technique is still required. Transfusions can hamper precise classification although the variant is detected.	Useful as the first-line screening technique for non-resource constrained settings.
Automated capillary zone electrophoresis [7,37,37,59–62]	Identifies peaks as low as 1-2% migrating in the zone(S). Performance has been comparable to CE-HPLC for sickle cell disorders in nearly all studies.	High resolution, rapid, low sample volume, backed-up by a significant body of literature, fully automatable, very high throughput, no additional requirement for a densitometer. β-thalassemia, HbH and variants detected in one procedure. Separates HbE/A2/Lepore. A2 estimation is more accurate than CE-HPLC in samples containing HbD or HbS. Identifies Hb Constant Spring, Hb Bart's, HbH even when present in minute quantities.	Capital intensive. Requires trained manpower and expertise. Second confirmatory technique is still required. Transfusions can hamper precise classification although the variant is detected.	Useful as the first-line screening technique for non-resource constrained settings.
Agarose gel electrophoresis at alkaline pH [4,5,7,25,37–40]	Used as the main technique in most older studies prior to advent of CE-HPLC. Bands of up to 5-10% are easily visualized by most techniques and can be quantitated densitometrically.	Relatively inexpensive. Offers clear interpretation in most cases. Manual methods are available for low resource settings.	Co-migration of HbD, G, Q-India, Lepore make it non-specific by itself. Second confirmatory technique is still required. Technically cumbersome despite automation as most instruments are not truly walk-away. Densitometric quantitation is insufficiently robust to diagnose β-thalassemia trait. Transfusions can hamper precise classification although the variant is mostly detected.	Useful mainly as a confirmatory technique; difficult to apply as a first-line screening or diagnostic test.

TEST NAME	ACCURACY INDICES	ADVANTAGES	LIMITATIONS / PITFALLS	ROLE IN TESTING
Isoelectric focussing [7,60,61,63,76]	Shows 100% concordance to CE-HPLC for variant haemoglobins in a Tunisian study.	High resolution. Can be semi-automated.	Technically cumbersome. Relatively expensive. Multiple bands may make interpretation difficult. Transfusions can hamper precise classification although the variant is detected. Quantitation of low-level fractions can be erroneous by densitometry.	Difficult to apply as a first-line testing modality; may be used for secondary confirmation by advanced and/or research laboratories.
ARMS-PCR or PCR-RFLP for DdeI restriction enzyme site obliteration [7,54,59,77–79]	Reported sensitivity/specificity for ARMS-PCR is 75% to 92.5%/100%, while for PCR-RFLP is possibly similarly high.	Yields a definitive diagnosis, mandatory for prenatal testing. Helps resolve confusing cases that are post-transfusion, or if parental studies are not available.	Low throughput. Require molecular laboratory set-up. More expensive and technically cumbersome than protein separation techniques. Polymorphisms at priming sites may cause false negatives. Maternal contamination is a concern in prenatal diagnosis. Proper controls are essential, for e.g., a large deletion on the partner allele may give a false homozygous pattern.	Sufficiently accurate for use in prenatal diagnosis.
Covalent reverse dot blot hybridization assay [5,79–82]	92.5% sensitivity and 100% specificity for β-thalassemia mutations.	Technically straightforward. Inherent multiplexing. No specialized interpretation skills are required. An NIIH-ICMR designed kit is available that screens for common Indian β-globin gene mutations: IVS 1 nt 5 (G>C), IVS 1 nt 1 (G>T), CD 8/9 (+G), CD 41/42 (-CTTT), CD 15 (G>A) and CD 30 (G>C) along with HbS and HbE variants.	Inflexible format of pre-prepared strips, if purchased commercially. Closely located mutations may interfere with each other's detection – awareness of patterns is required.	Suitable for medium complexity labs to verify screen detected cases; has been used for prenatal diagnosis.
High-resolution melting curve analysis [83]	Reported sensitivity/specificity are 97.5%/99.7%.	Accurate. Relatively low cost.	Low throughput. Requires real-time PCR instrument and molecular biology lab set-up. Technical expertise is necessary. Polymorphisms at priming sites may cause false negatives. AS (trait) may not be distinguished from SC state (compound heterozygous).	Sufficiently accurate for use in prenatal diagnosis. Primer design is critical for assay success.

TEST NAME	ACCURACY INDICES	ADVANTAGES	LIMITATIONS / PITFALLS	ROLE IN TESTING
Direct DNA (Sanger) sequencing [4,7,63]	Used as a gold standard for genotypic studies on β-globin.	Highly accurate for germline disorders caused by point mutations and small indels. Assesses the entire amplified region, and not only the sickle substitution.	Deletions are not detected. Interpretation requires knowledge of polymorphisms, artifacts and background clinical and routine test data. Very capital intensive. Technically demanding. Instrument maintenance is critical.	Sufficiently accurate for use in prenatal diagnosis and as a confirmatory test for other molecular techniques.
Immunochromatographic lateral flow assays [48,84,85]	Typically, 100% specificity with over 95-99% specificity.	Relatively inexpensive. Rapid.	Do not detect other Hb Variants or differentiateSS from Sβ-thalassemia. Misinterpretation in cases of recent transfusion.	Suitable for point-of-care applications.
Paper-based haemoglobin solubility assays [41–43]	100% sensitivity and 83% specificity in neonatal screening.	Cheap, diagnostically robust, easy to interpret. Rapid (20 minutes). Low sample volume. No power source required. Room temperature storage of reagents.	Interference by microclots. Operator-based interpretation may be subjective, esp. for heterozygotes. Newborn testing needs rigorous validation.	Promising technology for field and point-of-care applications.

CLINICAL EFFECTS OF VARIOUS COMPOUND HETEROZYGOUS COMBINATIONS WITH THE SICKLE CELL HAEMOGLOBIN

Interpretation of the clinical significance of coinherited variants requires knowledge of their interactions from literature and clinical experience. Due to the multiple genotypic influences that make the sickle cell disorders behave more like polygenic traits (despite being a monogenic disorder), due caution and appropriate disclaimers are advised while counselling patients about the expected clinical phenotype in any particular genotype, especially when dealing with rare combinations. Some general pointers are offered below:

SICKLE CELL DISEASE, I.E., DELETERIOUS STATES ARE CAUSED BY

- Sickle cell anaemia (homozygosity for HbS).[10]
- Compound heterozygous states for HbS with β-thalassemia, HbD-Punjab, Hb Lepore, Hb C, and with the rare variants of haemoglobins C-Harlem, O-Arab, Hofu etc.[7,9,11]
- Heterozygosity for Hb S-Antilles, Hb S-Oman, and Hb Jamaica Plain.[7,86]
- Compound heterozygous state for HbS with δβ0 thalassemia (milder than SS state due to higher fetal haemoglobin).[7,87]

ASYMPTOMATIC OR MINIMALLY SYMPTOMATIC COMBINATIONS WITH HAEMOGLOBIN S ARE

- Compound heterozygous state for HbS with haemoglobin D-Iran.[7,88]
- Compound heterozygous state for HbS with haemoglobin E.[89]
- Compound heterozygous state for HbS with hereditary persistence of fetal haemoglobin.[87]
- Combinations of HbS with α-globin chain variants (it is in general, but not always asymptomatic).
- β-thalassemia mutation in cis with a βS mutation.

DISTINGUISHING SICKLE CELL ANAEMIA FROM SICKLE β-THALASSEMIA

This is often a major diagnostic decision in CE-HPLC or CZE reporting. While definitive conclusions can only be derived from parental testing or, more laboriously, from molecular genetic assays, a few pointers in routine studies are as follows:[7,39,54]

- Hypochromic microcytosis, an elevated HbA2% (4.0-5.6%) and persistence of significant splenomegaly beyond adolescence favour sickle β-thalassemia.
- Normocytic normochromic red cell indices and normal range HbA2% (1.6-3.6%) favour (but do not prove) sickle cell anaemia (SS state).

ROLE OF FAMILY STUDIES AND CASCADE SCREENING

Parental studies in the form of haemogram and CE-HPLC or CZE are invaluable in resolving diagnostically difficult cases. Parental samples are important even when genetic analyses are available, to dissect the intricacies of the several genotypic modifiers of disease phenotype. In case parental samples are unavailable, those of other first-degree relatives (siblings, children) or less helpfully, the extended family may be tested.

Discovery of a proband with a clinically significant haemoglobinopathy must prompt the clinical advice to get as many blood relatives screened for haemoglobinopathies as feasible. This enables detection of further asymptomatic carriers who can then participate in informed reproductive decision-making at the appropriate time points.

NEWBORN SCREENING FOR SICKLE CELL DISORDERS

In view of evolving national policy of hospital-based childbirth, neonates comprise an easily targeted population in high-risk areas, and screening should be done. However, this should be guided by individual state governments depending on the policy, requirements and resources available. The cases positive by the screening test must be confirmed at the end of 6 months. Considering its cost effectiveness, logistic challenges and technical advantages, the task force considers this NBS as an additional tool to assess the effectiveness of any public health control programme (baseline values vis-à-vis values post-intervention). Parents of newborns detected by screening may opt for prenatal diagnosis in subsequent pregnancies. [14,31,40,64,65]

CHOICE OF TARGET POPULATION FOR NEWBORN SCREENING

From an epidemiological perspective, a screening programme targeting high-risk areas appears more feasible in the Indian setting. Prior efforts in the form of large pilot studies have been concentrated in the states of Gujarat, Maharashtra, Chhattisgarh, Odisha and Madhya Pradesh . [14,31,90–93,93–95] Strategies may focus on babies of women detected to be carriers previously, to optimize resources. Specimens include cord blood of supervised births, or heel prick or other samples from babies where cord blood collection has not been done.

Choice of technique for newborn screening. From a laboratory perspective, several techniques like CE-HPLC and Capillary Zone Electrophoresis can be used for newborn screening with their inherent advantages and drawbacks. Large studies have used CE-HPLC & CZE as the initial tool (moving away from isoelectric focussing used in the past).[14,91,92] However, they require sample transfer to central laboratories. Among the new point-of-care devices, immunochromatographic lateral flow assays have been shown to fulfil the requirements for a non-electricity dependent, simple assay where results are available rapidly (before the mother and baby leave the testing site).[95–97]

ROLE OF INTEGRATED SCREENING FOR MULTIPLE HAEMOGLOBIN DISORDERS PREVALENT IN INDIA

The immense genetic diversity of the Indian subcontinent is equally reflected in the plethora of haemoglobin disorders that occur in our country. Various thalassemic alleles and haemoglobin variants of all types are present in polymorphic frequencies in the Indian population. While a regional and ethnic distribution is found for many of these, screening for only one or two common variants in the subject's community or region is no longer feasible both logistically as

well as in face of increasing mobility, intermarriages and general awareness.

In such a scenario, for this guideline to advocate the most appropriate test for screening for all significant haemoglobin disorders is very challenging. Taking the β-thalassemias, HbS and HbE as epidemiologically as well as clinically the most significant haemoglobin diseases in India, the close to optimal tests in a completely non-resource restricted setting even for screening could be CE-HPLC and CZE. In large urban centres and for patients with adequate resources, one or the other of these two are already being used as part of mandatory or voluntary testing in pregnant women coming for their first antenatal visit. Governmental programmes like the National Health Mission are attempting to increase the penetration of CE-HPLC-based diagnostics into the more remote areas.[4,5,98]

However, in light of the reality of resource, infrastructure and expertise constraints across large swathes of India, in the absence of CE-HPLC or A-CZE, other options must be examined. A combination of tests to screen for HbS (sickle solubility test, or paper-based haemoglobin solubility assays), β-thalassemia - hemogram analysis for hypochromic microcytosis,(i.e., MCV ≤80 fL and/or MCH ≤27 pg) coupled with analysis of anisocytosis/poikilocytosis (RDW-CV <14%) (99,100) and, in high frequency regions, the dichlorophenolindophenol (DCIP) test to screen for haemoglobin E heterozygosity, homozygosity or compound heterozygosity E-β thalassemia may be feasible. The DCIP test is inexpensive, technically simple and was recently shown to have a sensitivity/specificity of 96.4%/97.4%. [(101)] Red cell indices including alow MCV of <80fl, or indices-derived formulae can be considered as a broad screening test for HbE states in a resource-constrained set up, with patients being confirmed by A-CZE/CE-HPLCS.[99,100]

MOLECULAR DIAGNOSTIC TESTING

The single nucleotide substitution that gives rise to haemoglobin S can be reliably and relatively easily confirmed at a molecular genetic level by genomic DNA testing. This is however, not required in the vast majority of cases, as a combination of at least 2 non-molecular techniques can robustly clinch the diagnosis just as accurately, but at much lower cost and technical complexity.

INDICATIONS FOR GENETIC TESTING IN A SICKLE CELL DISORDER ARE:

1. Prenatal diagnosis. Molecular genetic confirmation is mandatory when determining the genotype of a fetus in a couple-at-risk.
2. Ambiguous diagnosis. In several situations, the CE-HPLC/CZE along with a second technique may not clinch the diagnosis, necessitating molecular testing. Examples include:

a. Testing done on a recently transfused, or frequently transfused patient, especially when one or more parents is/are unavailable. In such a situation, distinction between SS and Sβ, or indeed sickle cell trait with an unrelated cause for anaemia cannot be ascertained.

b. Clinical discordance with routine test results, for e.g., severe symptoms in an apparent sickle cell trait on CE-HPLC (seen, for e.g., in haemoglobin S-Antilles, S-Oman or S-Jamaica Plain where another mutation is inherited in cis with HbS(86); or alternatively, when S-traits show sickling crises due to coinherited pyruvate kinase deficiency)(102), or unusually mild or no symptoms in a patient with predominantly HbS+HbF on electrophoresis. The last is seen in sickle-β-thalassemia where the coinherited thalassemic allele is a β++ one.[54]

c. Laboratory test discorrelation, for e.g., sickled red blood cells are seen on blood smear, but electrophoretic mobility/CE-HPLC retention time of the variant seen do not correspond to HbS. This is the case in Hb C-Harlem, where, in addition to the substitution of valine for glutamic acid at position 6, there is another β-chain substitution at position 73 (asparagine to aspartic acid) that is the same as Hb Korle Bu. C-Harlem migrates with HbC on alkaline pH electrophoresis, but gives a positive sickle solubility test and sickles RBCs.[103]

MOLECULAR TESTS FOR THE SICKLE CELL MUTATION

The commonly performed tests for detecting the sickle hae-

moglobin mutation in DNA specimens are listed and discussed in Table 2. It is important for testing laboratories to be aware of strengths as well as pitfalls of the assays they employ, including false negative rates. Some salient points to be aware of are:

1. Some patients with sickle-β-thalassemia may have a thalassemic mutation that lies close to the restriction/HbS site, like the codon 5(-CT) [HBB:c.17_18delCT]. This can lead to a loss of the DdeI restriction site, giving a pseudo-homozygous pattern on PCR-RFLP suggesting sickle cell anaemia. ARMS-PCR for HbS shows the correct heterozygous state for HbS.[54]
2. ARMS-PCR testing must always include primers for both the wild-type and mutant alleles, even if the CE-HPLC appears to be a clear-cut case of sickle cell anaemia. This is because a large deletion on the homologous chromosome 11 can give rise to the PCR with the mutant primer giving a false apparently homozygous pattern.[104]
3. Presence of a neutral polymorphic variation at the primer binding site, especially if close to its 3' end, can lead to non-amplification in RFLP as well as ARMS-PCRs.[105]
4. High-fidelity Taq polymerase with exonuclease/proof-reading activity should not be used in ARMS-PCRs.[(105)]
5. In ARMS-PCR, annealing temperatures should be set high, depending upon the primer, and PCR cycle number should be lower, to prevent non-specific amplification.[106,107]
6. ARMS-PCRs may show false-positive results due to non-specific amplification, hence, positive, negative and internal controls are important.[105]

GENETIC MODIFIERS OF DISEASE PHENOTYPE

Sickle cell anaemia and compound heterozygous states like sickle-β-thalassemia show marked phenotypic variation.[30,54,108] The genetic basis of this heterogeneity has been studied in detail, and the salient modifiers are listed in Table 3. Routine testing of these genetic loci is however not currently indicated.

TABLE 3 - GENETIC MODIFIERS OF PHENOTYPIC VARIABILITY IN SICKLE CELL DISORDERS

β globin gene haplotypes that can be determined by analysis of restriction fragment length polymorphisms or sequencing. The 5 common haplotypes are: Arab-Indian, Senegal (both with high HbF), Bantu/Central African Republic (with lowest HbF), and Benin and Cameroons haplotypes with moderate HbF levels.[30,32,89,109]		
Coinherited α-thalassemia reduces hemolysis, end-organ damage, leg ulcers, stroke, splenic dysfunction and priapism. [(7,30–32,55,89)]		
Enhancement of fetal haemoglobin (HbF) production by:[15,30,110,111] 1. mutations / polymorphisms in the β-globin gene cluster: For e.g., co-inherited deletional HPFH, δβ-thalassemia, Gγ-158(C>T)-Xmn1 polymorphism, β-thalassemia mutations in the promoter region, or, 2. Single nucleotide polymorphisms in quantitative trait loci in other non-globin genes: For e.g., HBS1L-MYB intergenic region on 6q23, BCL11A gene on 2p16, or KLF1 on chromosome. [19p13]		
Nature of mutations in the β-globin (HBB) gene (β0, β+, β++) in case of sickle-β-thalassemia.[54]		
Genes unrelated to haemoglobin production that influence the onset and severity of other complications like thrombosis, bone disease, jaundice, gallstones, and iron overload. Some examples are listed below:		
Organ system or metabolic pathway affected	**Tertiary genetic modifiers of phenotype including commonly studied variants**	**Observed phenotypic variation(s) or complication(s)**
Coagulation pathways. [112–114]	Factor V Leiden, MTHFR C677T, and prothrombin G20210A.	Hemostatic changes including those in platelets, endothelium, leukocytes, the clotting cascade, and, the natural anticoagulant systems. Increased frequency of thromboembolic events (cerebrovascular, DVT, PE etc.).
Myocardial dysfunction. [115]	Apolipoprotein E, ε4 allele.	Left ventricular cardiac failure.
Bilirubin metabolism.[33]	Polymorphism of the promoter region of bilirubin UDP-glucuronosyl transferase (UGT1A1) [TA7/TA7 genotype].	Jaundice, indirect hyperbilirubinemia, cholelithiasis.

PRENATAL TESTING

Prenatal diagnosis as a component of a prevention programme for sickle haemoglobinopathies provides an option for couples at risk (i.e., when both partners are heterozygous for a haemoglobinopathy or thalassemia) for terminating affected fetus.

TECHNIQUES OF FETAL DNA SAMPLING ARE:[77–79]

- **Chorionic villus sampling (CVS)** is usually performed in 10-14 weeks of gestation. It reduces the emotional stress as well as the complications associated with 2nd trimester diagnosis. CVS is a good source of fetal DNA, permitting rapid results.
- **Amniocentesis** is done between 14-16 weeks of pregnancy. ~20-35 mL of amniotic fluid is aspirated and centrifuged to obtain sufficient fetal DNA from fetal-origin amniotic cells.

DNA extracted from the above specimens is tested for inheritance of parental mutations using any of several techniques including ARMS-PCR, reverse dot blot assay, PCR-RFLP etc. Choice of molecular technique depends on local resources, expertise and mutational spectrum observed.

Correlation of fetal sample results with parental specimens run in parallel is important. Maternal contamination must be excluded if solely the maternal allele is detected. This is most often done by analysis of variable number of tandem repeats (VNTRs) by PCR followed by agarose gel resolution or by fluorescent capillary electrophoresis-based fragment length analysis. VNTRs are highly polymorphic genomic markers that are used for paternity testing, gene mapping, identity confirmation etc. Markers used routinely for this purpose include Apo B, D1S80, ACTBP2 and Ig-JH.[116–118]

Invasive techniques carry a 0.5-2.0% risk of fetal loss. Non-invasive diagnostic procedures avoid risk of miscarriage and are based on isolating and analyzingfetal cells or circulatory cell-free fetal DNA in the maternal circulation.

NIPT for sickle cell disorders has been tested in Indian settings independently as well as in collaboration with advanced laboratories and analytical sensitivities have ranged from 92% to >98% with specificities of >99%.[79,119,120]

GENETIC COUNSELLING AND ETHICS IN THE LABORATORY CONTEXT

Issues of consent for testing, confidentiality of results, data safety, prevention of stigmatization, autonomy in reproductive choices and the possibility of discovering mis-paternity are inherent to laboratory testing, and should be reflected upon and SOPs decided at the initiation of testing. A trained genetic counsellor should be available at either the clinical end or affiliated to the laboratory for couples at risk, and those undergoing prenatal diagnosis. In the absence of the above manpower, the haematologist, paediatrician, physician or obstetrician must discharge the duties of educating and informing the subject of the implications and interpretation of sickle cell disorder testing.[4,5] For persons discovered incidentally on HbA1c testing to have sickle cell trait, most have no reservations about further confirmatory testing, which can be done reflexly.[19]

RECOMMENDATION:

1. Test selection, performance and reporting must always be tailored to the patient's clinical background, healthcare setting and testing scenario.
2. In addition to clinically suspected cases, testing for the sickle haemoglobin should be conducted in all available blood relatives of a patient known to have a sickling disorder. Cascade screening of extended family members must be encouraged.
3. All screen-detected cases of sickle cell disorders should be subsequently confirmed by a diagnostic test using an independent technology.

4. Point-of-care rapid tests like paper-based haemoglobin solubility assays and immunochromatographic lateral flow assays are suitable for screening followed by confirmation using standard assays like CE-HPLC Automated capillary zone electrophoresis.
5. High-performance liquid chromatography (CE-HPLC) or Automated capillary zone electrophoresis (A-CZE) are recommended for diagnostic use in non-resource-constrained hospital or diagnostic laboratory settings.
6. HbS or another variant haemoglobin detection by any technique must be considered presumptive until its identity is verified through a second technique based on an independent principle.
7. Parental studies of hemogram and CE-HPLC or A-CZE are invaluable in resolving diagnostically difficult cases, even when genetic analyses are available.
8. Discovery of a proband with a clinically significant haemoglobinopathy must prompt the clinical advice to screen as many blood relatives as feasible for haemoglobinopathies. This enables detection of further asymptomatic carriers who can then participate in informed reproductive decision-making at the appropriate time points.
9. For settings lacking CE-HPLC or A-CZE, screening for a single haemoglobinopathy is often not clinically realistic. A minimal integrated screening panel combining tests for HbS (sickle solubility test, or paper-based haemoglobin solubility assays), β-thalassemia (hemogram analysis for microcytosis, i.e., MCV ≤80 fL and/or MCH ≤27 pg) and, in high frequency regions, red cell indices or the dichlorophenolindophenol (DCIP) test to screen for haemoglobin E are recommended.
10. Molecular genetic studies are rarely required in routine clinical practice but are mandatory for prenatal testing and can help resolve confusing cases, especially post-transfusion, or if parental studies are not available.
11. Prenatal diagnosis as part of a prevention programme for sickle haemoglobinopathies should be conveniently available as an option for couples at risk at an advanced centre with sufficient expertise and availability of appropriate genetic counselling for this purpose.
12. Considering the magnitude of population and required logistics, the Taskforce unanimously recommends screening tests for common prevalent haemoglobinopathies (HbS, β-thalassemia and HbE). The positive cases detected by any screening test should be subjected to CE-HPLC or capillary zone electrophoresis for confirmation. Whenever required, evaluation of both the parents, and, or, genetic mutation study may be taken up.
13. Screening test for sickle cell disease could be a paper-based haemoglobin solubility test, the sickle solubility test or another point-of-care assay. For β-thalassemia screening, cell counter-derived red cell indices (MCV <80fl, MCH <27 pg) are useful, and for HbE, screening could be done using the DCIP test, and/or, a very low MCV of <80 fl.
14. The Taskforce strongly recommends a package of screening tests in any public health screening programme of the Government to detect common haemoglobin disorders like SCD, Beta-Thal and HbE. This will be immensely beneficial from logistic point of view along with feasibility.

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CHAPTER 3

Clinical Presentation

A suspected patient with sickle cell disease (SCD) will most commonly present with varied clinical manifestations such as persistent pallor, pain, fever, lethargy and jaundice. Sickle cell disease may presents with acute and chronic complications.

THE MAJOR ACUTE COMPLICATIONS OF SCD INCLUDE THE FOLLOWING

a) Infections.
b) Severe anaemia (may be due to splenic sequestration, aplastic crisis, or hyperhemolysis).
c) Vaso-occlusive phenomena presenting as acute vaso-occlusive pain, stroke, acute chest syndrome, renal infarction or medication toxicity, dactylitis or bone infarction, and Myocardial infarction.
d) Complications related to pregnancy including spontaneous abortions, still births, IUGR. Priapism, venous thromboembolism are also common.

Major chronic manifestations as chronic pain, anaemia, neurologic deficits or seizure disorder, pulmonary conditions including pulmonary hypertension, renal impairment, osteoporosis, bone infarction, cardiomyopathy with diastolic dysfunction, hepatotoxicity and pigmented gallstones, chronic leg ulcers and proliferative retinopathy.

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 anaemia. The most common complication of SCD is an acute episode of severe pain referred to an acute VOC involving target organs such as bone, spleen, liver, kidney, lung and brain.

The severe sickle cell painful crisis that requires hospitalization in adults typically seems to evolve along four distinct phases: prodromal, initial, established, and resolving. Each phase may to be associated with certain clinical and laboratory findings and lasts approximate 10 to 12 days.

PREDISPOSING FACTORS FOR SICKLE CELL CRISIS

These include exposure to cold/drenched by rain, physical exertion, dehydration, injury (including surgical injury), psychological stress, idiosyncratic (peculiar to the individual), idiopathic (unidentified), Infections/ infestations.

INITIAL EVALUATION OF A SCD PATIENT IN CRISIS

These should include history of pain, self-assessment of pain, and prior treatment taken before arrival at the hospital.
a) History of usually effective analgesics.
b) Drug allergies.
c) Assessment of vital signs: blood pressure, heart rate, respiratory rate, oxygen saturation (administer oxygen if O2 saturation<90%) and temperature.
d) History of increasing jaundice and passage of coke-coloured urine.
e) Assessment of areas of bone tenderness.
This is very much essential to establish and treat the disease.

SCD AMONG INDIAN PATIENTS

There is considerable heterogeneity of manifestations in SCD in India. Many factors contribute to this heterogeneity. The factors are Hb-F levels and coinheritance of alpha thalassemia, interaction with beta C gene and b-thalassemia gene. Indian patients with SCD behave like Arab Indian haplotype with mild clinical presentation as compared to Africans.

SCD in India is associated with high and early mortality.[8-11] A Study from Aboriginal Community

from Tamil Nadu reported 22 deaths out of 157 patients (14.01%) in 10-year follow up. The median age of death is 25 years which was 20 years less than the non SCD population. Acute chest syndrome (ACS) is one of the important reasons for death 7/22 patients.[8] In a study conducted in Madhya Pradesh among 776 patients followed up from 2010-2014, 81 patients (10.4%) had died during the period. Hepatic failure and splenic sequestration were predominant causes of death.[9] In a case-control study from Odisha, 22 deaths (cases) with 44 alive patients (controls) in 1 year were studies.[10] Another autopsy study from Gujarat, with 679 autopsy cases 25 cases with SCD were reported.[11] In both the studies mortality peaks in 2nd and 3rd decade with median age of death 20 to 30 years. Major cause of death remains, complicated VOC especially ACS, Sudden Death, and infections. Pain episode is associated with 60-70% of death in SCD patients.[10-11]

SCD is associated with organ complications occurring very early in life. Neurological complications are common among Indian patients and seen as early as <20 years.[12,13] Neurological complications is seen in approximately 10% of patients (stroke, seizures).[12-15] Silent cerebral infarct was seen in additional 10% of cases and 1/4th of the children with SCD in India showed abnormal findings in TCD.[14,15] There was also a substantial reduction in IQ, borderline intellectual disability & mild MR observed in SCD children compared to controls.[16] Renal complications are common among Indian patients and observed as early as <20 years of age.[17-18]

The magnitude of renal dysfunction was observed in 30% of the patients. Seventeen Cardiopulmonary complications are observed as early as <20 years of age. Pulmonary Hypertension is prevalent in over 1/3rd of the pediatric patients.[19-20]

Vaso-Occlusion is the hallmark of SCD. Vascular dysfunction, inflammation, and P-selectin mediated cell-to-cell and cell-to-endothelium adhesion play an important role in the pathophysiology of SCD.[16,21-23] VOCs associated with a higher risk for death (Time to death HR=1.56; 95% CI [1.19-2.05]) and complications including ACS,(Time to ACS HR=58.67, 95% CI [50.21-68.55]) stroke (Time to stroke HR = 2.26, 95% CI [1.94-2.63]), pulmonary embolism(Time to PE HR=2.82, 95% CI[2.21-3.58], splenic sequestration (Time to splenic sequestration HR=43.99, 95% CI[30.65 – 63.13]) and pulmonary HTN (Time to Pulmonary HTN HR=4.12, 95%CI[3.14-4.41].[24] Vaso-occlusive crises are a common and repeated cause of morbidity and hospitalizations among sickle cell disease patients. Approximately 50 to 80% of Hospitalization in SCD are due to VOC.[16,25-30] VOC is the most common cause of mortality among Indian patients and substantially reduces the life span.[8-11] VOC substantially reduces the Quality of Life (QOL) of patients living with SCD.It also affects work, productivity along with sleep and daily activities.[31-34]

CLINICAL PRESENTATION OF SCD PATIENTS AMONG VARIOUS COHORTS IN INDIA

NEWBORN COHORT FOLLOW UP [35]

The age at first clinical presentation varied from 1 month to 5 years. All painful events do not lead to VOC, pain and VOC were considered as separate complications. Pain followed by acute febrile illness and severe anaemia with blood transfusion requirements were the major complications. Some are presented with severe clinical complications, such as sepsis and severe vaso-occlusive crisis requiring frequent hospitalization.

NON-NEWBORN COHORT STUDIES [36]

The presenting signs and symptoms at the time of early clinical manifestation were often fever, joint pain, musculo-skeletal pain, anaemia, jaundice, and chest infection. It was observed that 44.3% of SCA and 35.9% of SB patients had first appearance of signs or symptoms of the disease prior to attaining the age of 3 followed by 3–6 years.

Recently the Clinical manifestation of sickle cell disease in India was reviewed by Dr Dipty Jain and Dr Dipika Mohanty.[37] The common clinical manifestations in SCD India are described below.

ANAEMIA AND SPLENOMEGALY

Double heterozygote SCD such as sickle beta thalassemia and SD thalassemia are common in some parts of India. They are often associated with severe anaemia, requiring more frequent blood transfusions.

Anaemia in Indian SCD children is multi-factorial, apart from nutritional deficiency (iron, Vitamin B12 folic acid deficiency), malnutrition, infections and parasitic infestations are common and should be corrected along with sickle cell disease. Usually, aplastic crisis is rare in Indian SCD.

In Indian SCD patients, the spleen is larger and preserved for longer duration. Indian SCD patients continue to have splenomegaly during the second decade. Persistent splenomegaly is more common in Sb thalassemia than SS. The transfusion requirements are also more in Sb thalassemia.

ACUTE CHEST SYNDROME

The prevalence of acute chest syndrome in Indian was not well studied. Sometimes the acute chest syndrome may be associated the respiratory tract infections.

INFECTIONS

Infections are important and most common causes for hospitalization in SCD children. In India, Staphylococcus aureus, Salmonella, Klebsiella and Escherichia Coli are the most common infections. Sickle cell gene protects against Plasmodium falciparum infections, higher HbF is not associated with better prognosis in SS patients in India.

STROKE

SCD children may suffer from stroke by 5 years of age and in some Indian cohort's stroke is rare. Sometimes the SCD was diagnosed after an episode of stroke in India.

DACTYLITIS

The prevalence of dactylitis varies significantly across different geographical regions in India.

PRIAPISM AND LEG ULCER

Priapism and leg ulcers are not uncommon in SCD patients from India.

AVASCULAR NECROSIS OF HIP

SCD children from India develop avascular necrosis (AVN) of hip usually by the second decade of life.

RENAL INVOLVEMENT

Glomerular hyper filtration is more common during the first decade, whereas renal insufficiency increases during the second decade in Indian patients.

PREGNANCY OUTCOME

The rate of still birth and low birth weight and preterm delivery was three times higher in SCD than non-SCD in India.

CONCLUSION

Sickle cell disease is a complex disease with genotype and phenotypic heterogeneity associated with several acute, chronic, and acute-on chronic complications leading to several end-organ damage and life-threatening complications. In the last decades, the knowledge of SCD pathophysiology has grown with an improvement in care and life expectancy. Care of SCD is highly complex and requires a multidisciplinary team approach. The role of the haematologists and sickle cell specialists is very important.

OBSERVATIONS:

1. Considerable heterogeneity of clinical manifestations of SCD India.
2. Most common complication of SCD is an acute episode of severe pain referred to an acute VOC.
3. Approximately 50 to 80% of hospitalization in SCD are due to VOC.
4. The age at first clinical presentation varied from 1 month to 5 years.
5. Anaemia in Indian SCD children is multifactorial. Nutritional deficiency (iron, Vitamin B12 folic acid deficiency), malnutrition, infections and parasitic infestations are common.
6. Indian SCD patients continue to have splenomegaly during the second decade of life.
7. The prevalence of acute chest syndrome in Indian SCD was not well established by studies.
8. Infections are important and most common causes for hospitalization in SCD children.
9. Neurological complications are common among Indian patients and seen as early as <20 years of age.
10. Pulmonary hypertension is prevalent in over 1/3rd of the pediatric patients.
11. SCD in India is associated with high and early mortality.

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CHAPTER 4

Management In Stable Condition

Sickle cell disease (SCD) refers to all disease genotypes, including SCA and compound heterozygous conditions, such as Hb SE, HbSβ+-thalassemia ,HbSD , HbS alpha thalassemia and HbS/HPFHHbSC, HbSD.

Depending on the underlying genetic conditions, the phenotype varies and therefore the sickle cell syndromes have heterogeneous presentation.

Sickle cell disease encompasses different states which may be acute and chronic or stable. The problems that can arise during stable conditions include chronic pain which can affect the day to day life of the patient including absence from school and from work, infections, deficiency disorders and others.

Pain is the commonest symptom of SCD and it can be acute, chronic, or acute on chronic types. Chronic pain is the predominant symptoms in stable condition. Smith and colleagues[1] in an analysis of pain diaries of 232 adults with SCD reported pain in 54.5% of the more than 30,000 days entered in the daily pain diaries. One significant observation of this study was that patients went for medical care in only 3.5% of 30,000 days.

OBJECTIVE OF MANAGEMENT OF SICKLE CELL IN STABLE CONDITION

- Prevention of pain episodes and minimization of acute events, prompt and adequate treatment of infections, prevention of complications and counselling so that the patient gets a good quality of life and school-going children lead a normal life and get education at par with a normal child of his or her age.

STRATEGY TO ACHIEVE THESE OBJECTIVES

- HU for all age groups
- Vaccination and antibiotic prophylaxis
- Supplementation of folic acid, vitamin D, calcium, methylcobolamine, zinc and iron (in presence of iron deficiency)
- Lifestyle modification which includes avoidance of stress, strain, exertion, avoidance of dehydration and extreme climatic condition to minimize acute complications
- Early management of an infection

PREVENTION OF PAIN EPISODES AND ACUTE COMPLICATIONS

Hydroxyurea (HU) is the key drug for treatment of sickle cell disease in stable condition and is established as the safe and effective treatment of SCD. It increases fetal haemoglobin which in turn retards gelation and sickling of RBCs. It also reduces the levels of circulating leukocytes, which decreases the adherence of neutrophils to the vascular endothelium. As a result there is reduction in vaso-occlusive pain events and other vaso-occlusive complications. Thus, hydroxyurea improves quality of life of the patients as well as survival. It is especially useful for severe genotypes e.g. SCD-SS, Sickle Beta Thalassemia.

In 1998, hydroxyurea was the first FDA-approved medication for the treatment of SCD after it was proven to reduce frequency of pain crisis in adults. Hydroxyurea is an inhibitor of ribonucleotide reductase and, similar to RBC transfusions, reduces the relative HbS%. Hydroxyurea does this by increasing the production of β-globulin, which in turn increases the percentage of HbF (HbF%) in the blood.

Initial evidence for the efficacy of hydroxyurea in SCD came from studies in adults[2];studies in children (Baby Hug trial) and then in infants soon followed.[3,4,5.]

Observational Multicentre Study of Hydroxyurea (MSH),[1] in 299 individuals with SCD, hydroxyurea was compared with placebo. The study has observed improved survival, besides other benefits with a follow up of over 17 years and the results were as follows:[6,7]

- Never exposed – 5 deaths per 100 person-years
- <5 years exposure – 6.8 deaths

- 5 to 10 years – 4.4 deaths.
- 10 to 15 years – 1.8 deaths.
- ≥15 years – 0 deaths.

The study has concluded that there is a definite benefit on overall survival; several other studies subsequently validated this.[8]

A prospective clinical study [8] of hydroxyurea therapy from Greece with 17-year follow up which enrolled SCD patients older than 16 have shown similar results; the results showed reduction in frequency of painful episodes and ACS events, reduction in need for RBC transfusions, hospitalizations and significant improvement in survival when compared to conventional therapy.

The other benefits of hydroxurea were observed in social functions, pain recall, and general health perception within 2 years of the MSH study. The 17.5 year followup analysis also indicated continued safety and benefit of hydroxyurea. Fifteen years of pediatric data also has highlighted on the the safety and efficacy of hydroxyurea for young people (reviewed in Ware 2010).[12] Long-term observational studies suggest sustained beneficial effects of hydroxyurea for young people without significant myelotoxicity, adverse effects on growth, development and fertility or increase in carcinogenicity.[14,15,16]

Supporting evidence from 21 observational studies involving 3,378 adults, with followup periods of 24–96 months, was consistent in showing a reduction in pain crises (60–90%), hospitalizations (90–100%), and an increase in HbF (4–20%).

A meta-analysis to study the efficacy, effectiveness, and toxicity of hydroxyurea in children with SCD found that fetal haemoglobin levels increased from 5-10% to 15-20%; haemoglobin concentration increased significantly; hospitalizations decreased by 56-87%; and the frequency of paincrisis was also decreased.[17]

Additional benefit of hydroxyurea in decreasing stroke risk was observed in phase III multicenter international clinical trial in children as it could lower the elevated cerebral blood flow velocities. After a mean of 10.1 months, transcranial Doppler (TCD) ultrasound showed that mean velocity had decreased 15.5 cm/sec in patients receiving hydroxyurea but had increased 10.2 cm/sec in those on observation only (P=0.02).[18, 19]

Other benefits of hydroxyurea are improved general quality of life and daily functioning. These in turn may translate to better school attendance and fewer days lost from work. It is also cost-saving due to reduced number of hospitalisations (baby hug).

DOSE OF HU

The aim of hydroxyurea dosing is to give Minimum Effective Dose which can be increased to Maximum Tolerated Dose (MTD) if required. General principle of starting HU is to calculate the initial dose based on body weight. The dose is increased approximately every eight weeks by 5 mg/kg daily, to a maximum dose of 35 mg/kg daily or until one or more of the MTD parameters are reached.

The starting dose of 10mg/kg body weight has been found to be effective in three prospective studies from different parts of India. [20, 21, 22] A cohort of both pediatric and adult patients 129, 128, 60 with confirmed HbSS cases respectively each [18 years age, vaso-occlusive crisis] (2/years and/ or rate of transfusion 1–2 units/month) with no disease related end-organ damage were assessed prospectively. They were started on 10 mg/kg/day hydroxyurea along with other supportive care and followed up monthly for 1 year or more. Pain episodes (VOC) and transfusion requirement was lowered in 92% and 87% patients respectively. Therefore, it is recommended to start hydroxyurea on 10 mg/kg per day; patients with CKD, however, need 50% dose reduction.

Hydroxyurea is available as capsule; for infants and small children, the capsule can be opened and contents can be mixed with food. However, paediatric formulation is preferable.

HU DOSE ESCALATION AND TOXICITY

For any dose escalation of hydroxyurea, Absolute Neutrophil Count (ANC) should be should be >1000/microL, Absolute Reticulocyte Count (ARC)>100,000/microL and Platelet Count (PLT), should be>150,000/microL.

MTD is achieved when,any one of the the parameters

e.g. ANC 1500 – 3000/microL, ARC 80 – 100,000/microL or PLT 80,000 – 100,000/microL is maintained.
Hydroxyurea toxicity is to be considered when any of the above parameters are below the following ranges.

- ANC <1500/microL (<1000/microL if <2 years of age).
- ARC < 80,000/microL.
- PLT <80,000/microL.

The study from Odisha has observed that hydroxyurea given at fixed dose of 10mg/kg without escalation is effective, requires less frequent monitoring, easy to administer, economical, well tolerated with better compliance without significant adverse effects.

HYDROXYUREA DURING PREGNANCY & LACTATION

It is contra-indicated during pregnancy and lactation.
Refer to relevant chapter for more details

TOXICITY

Besides cytopenia, a patient on hydroxyurea can have skin and nail changes; reassuring the patient would help.

MONITORING WHILE ON HYDROXYUREA THERAPY

It is recommended that while on therapy the following parameters are to be monitored

- CBC with differential, PLT, and reticulocyte count every two to three months.
- Creatinine and liver function tests every 6 to 12 months
- Ferritin and HbF once per year.
- Urine pregnancy tests as appropriate.
- For hematologic toxicity, weekly CBC until resolution, then restart with a lower dose.

HOW LONG TO CONTINUE HYDROXYUREA THERAPY

Therapy can be continued as long as there are no adverse effects. However if response is not optimal, then compliance must be ensured. In case of no response even after good compliance and MTD for 6 months, then hydroxyurea can be discontinued. It has been recommended addition of erythroid-stimulating agent to hydroxyurea for suboptimal response.[22]

Before considering non responder to hyrdoxyurea, however the following factors are to be checked.

- Compliance.
- Check dose and duration: MTD for at least 6 months.
- Add Erithropoisis Stimulating Agents (EPO etc).
- Check for any iron b12 deficiency.
- If none, then to discontinue.

For more details about hydroxyurea, please also refer to other relevant chapters

BARRIERS IN USE OF HYDROXYUREA

It is very important to remove barriers of suboptimal use of hydroxyurea which has proven benefit in SCD and necessary measures are to be taken to remove these. The common reasons for suboptimal use of hydroxyurea are:

- Hesitancy among providers about the safety and efficacy of hydroxyurea.
- Patient concerns about carcinogenicity, teratogenicity.
- Compliance issues with daily dosing.
- Need for time to time clinical and laboratory monitoring
- No hydroxyurea solution for small children.
- Cost of the drug and non availability in remote areas.

OTHER MEASURES FOR PAIN MANAGEMENT IN CHRONIC STATE

L-GLUTAMINE ORAL POWDER

It was approved by UD FDA in children of 5 years or older with SCD in 2017[23]. L-glutamine increases the proportion of the reduced form of nicotinamide adenine dinucleotides in sickle cell erythrocytes; this probably reduces oxidative stress, which contributes to the pathophysiology of SCD.

In a randomized placebo controlled trial, it has been shown that patients on L-Glutamin had less pain epi-

sodes, fewer hospitalisations and fewer disease related complications.

CRIZANLIZUMAB

It is a P-selectin inhibitor and was approved by US FDA in 2019 in the treatment of SCD. It reduces the frequency of VOC in adults. The SUSTAIN clinical trial has shown that Crizanlizumab decrease pain episodes in both HU treated and HU untreated patients[24, 25]

VOXELATOR

It is a HbS polymerization inhibitor and improves Hb response. It was approved for treatment of SCD in 2019. [26]

OPTIONS WHEN NO CAUSE FOR CHRONIC PAIN IS IDENTIFIED

For adults who have SCD-related chronic pain with no identifiable cause beyond SCD, ASH suggests serotonin and norepinephrine reuptake inhibitors (SNRIs eg, duloxetine and milnacipran), tricyclic antidepressants (eg, amitriptyline), or gabapentinoids (eg, pregabalin) as options for pain management.

PREVENTION AND MANAGEMENT OF INFECTION

Patients with SCD are susceptible to both viral and bacterial infections; the infections are usually severe in presentation. Any fever or infection in a patient of SCD is to be treated as a medical emergency and immediate measures are to be taken. Patients and relatives should be counselled about importance of early detection and treatment of infection, which can otherwise be life-threatening.

Refer to relevant chapter for details

LEG ULCER

Chronic leg ulcer is seen in patients with SCD in stable conditions and can be persistent if adequate care is not taken. The best approach is to prevention; properly fitted shoes should be worn by the patients and should avoid injuries to the legs.

Once ulcer sets in, prompt care is to be given; elevation and rest to the limb, use of systemic plus topical opioids for relief of pain are few immediate measures. Some patients may need surgical intervention and rarely grafting.

NUTRITION

Taking care of nutrition in SCD children go a long way in giving good quality of life as well as their growth and development.

VITAMIN D & CALCIUM SUPPLEMENTATION

It has been shown patients with SCD are at higher risk of having vitamin D and calcium deficiency; the prevalence has been reported to range from from 33% to 100%. Vitamin D regulates calcium metabolism and is essential for bone mineralisation. The deficiency of it can lead to different musculoskeletal problems like muscle weakness, chronic bone pain, avascular necrosis, fragility of the bones and compression fractures. These can secondarily affect studies and work of the SCD patients. Even though strong evidence to recommend vitamin D and calcium supplement is lacking it is suggested to be supplemented in patients with SCD.[27]

FOLIC ACID

Folic acid is given widely once a diagnosis of SCD is made for lifelong; there is no scientific evidence of using folic acid, but it is suggested to be given to prevent folic acid deficiency due to chronic hemolysis and also for those patients who are on HU therapy.

ZINC

Zinc deficiency has been reported in both children and adults. Deficiency of Zinc in children with SCD is associated with decreased in height and weight, poor muscle mass,

and delayed sexual and skeletal maturation. Besides Zinc having an important role in immune defence, multiple randomised controlled studies have reported lower incidence of infection in patients with SCD when zinc supplementation was given. It has also been reported to reduce VOCs.[28]

IRON SUPPLEMENTATION

For those patients who have confirmed iron deficiency anaemia, especially a menstruating woman, iron can be supplemented in therapeutic doses to correct the anaemia due to iron deficiency. One study from Odisha has documented iron deficiency in roughly 10% of cases while similar number of patients did show the iron overload needing iron chelation therapy. [29]

IRON CHELATION

This is discussed in a specific chapter.

Monitoring during stable conditions: Regular monitoring of patients to prevent complication is an essential component of management of SCD in stable condition.
Refer to relevant chapter for details

SICKLE CELL TRAIT (SCT)

Patients with SCT have normal life–expectancy and do not suffer from VOCs in physiological conditions; however they can have hematuria due to renal papillary necrosis, it is usually microscopic; but gross hematuria can occur after heavy exercise. Measures to take are to increase fluid intake and to start

- Sodibicarbonate tab: 650-1200 mg/day.
- Anti-fibrinolytic agents if bleeding persists: clot colic can be however be precipitated on taking these agents.
- Regular Monitoring.

RECOMMENDATION:

1. Hydroxyurea should be started in all age groups (if no contraindications) at the dose 10 mg/kg/day. If required, the dose can be increased by 5 mg/kg/ every 8 weeks till MTD or up to dose of 35 mg/kg/day.
2. The dose should be titrated to maintain ANC of minimum 1500 per microL and PLT of >80,000 per microL.
3. Young females willing for pregnancy should discontinue hydroxyurea after discussion with their physicians. However it can be continued in selected cases if required after 1st trimester of pregnancy.
4. All the newer drugs for VOC (pain crisis) and other pharmacological agents used for pain relief like paracetamol, pregabalin, triptiline, etc., should be tried when there is sub-optimal response to MTD or intolerance to hydroxyurea.
5. Folic acid, vitamin D, calcium and zinc supplementation should be given in all cases.
6. Iron supplementation should be done if there is evidence of iron deficiency anaemia.
7. Fever or any other infection is to be treated as medical emergency and penicillin prophylaxis should be given to children.

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CHAPTER 5

Hydroxyurea Therapy

Sickle cell disease (SCD) is a progressively debilitating genetic disorder affecting approximately 5% of the world population, with a global burden of 2,75,000 newborns affected with SCD every year.[1] Of this burden, about 80% is from Sub-Saharan Africa, and almost 15% of world neonates with SCD are born in India.[2]

Several therapies and management protocols are available for treatment and management of SCD in other parts of the world, and they are proven to be safe and efficacious.[3-5] However, little was done in India to demonstrate the impact of these efficacious interventions. Although considerable research has been done in India, it is limited to screening and genetic research.[6] This research has very fewer implications on clinical practice and policy.

Hydroxyurea (HU), also known as hydroxycarbamide, therapy is one of the efficacious therapies for treatment of SCD. This review demonstrates the efficacy of HU in reducing adverse events among Indian SCD patients and improves their conditions. This review is purely based on studies conducted in India among Indian SCD patients.

METHODOLOGY

This section is based on the review of published papers that reported various kinds of interventions, primarily with HU therapy conducted in India to treat and manage SCD patients. These papers reported the data collected from Indian SCD patients were obtained by searching PubMed/Medline, Google Scholar, and Web of Science. The data from these papers were tabulated (Table 1). Heterogeneity was found across the sites in terms of patient characteristics, study design, treatment/intervention regimens and outcome indicators. The patients varied by age group. Concerning the intervention components, HU therapy, with or without other interventions, is used in most studies.Outcome indicators for assessing the impact of the intervention varied across the studies. These indicators are the incidence of vaso-occlusive crisis (VOCs), hospitalization (including the duration in some studies), blood transfusion and haematological parameters.

RESULTS

Out of 15 studies that dealt with HU therapy, 10 dealt with treatment with HU alone.[7-16] In other studies, combination therapy with HU was given. HU with folic acid was given in four studies,[17-20] and HU with folic acid and ibuprofen was given in another study.[21] Other than these 15 studies, three reported comprehensive care, including HU therapy.[22-24]

Concerning the dosage of HU, most of the studies followed the dosage of 10 mg/kg/day;[7,8,9,17,18,20] three studies adopted the dosage of 20 mg/kg/day,[11,21] and one study adopted the dosage of 15 mg/kg/day.[12] A study from Gujarat used the dosage from 15 mg/kg/day to 30/mg/day and built up the maximum tolerance dose (MTD) of HU.[13] Three studies did not mention the dosage and presumed they followed the dose of 10 mg/kg/day.[22,24]

IMPACT OF INTERVENTIONS

Various outcome indicators (alone or in combination) were used to assess the impact of HU therapy. Fifteen studies used the reduction of incidence of VOC,[7-9,10,12-18,22,23] 10 studies used the reduction of incidence of hospitalization,[7,8,12-15,18,20,22,23] 12 studies used some haematological parameters,[7-10,12-18,20] and 11 studies used reduction of need of blood transfusion.[7,10,12,13,15,17-20,22] A study among children assessed the impact of HU therapy on scholastic ability.[11] Another study by Jena and Swain[21] assessed the effect of HU therapy on avascular necrosis of the femoral head in adult SCD patients. One study assessed the safety of HU dosage.[13]

All studies reported positive and statistically significant improvement by HU therapy. Post-intervention data revealed a significant reduction in the incidence of VOC after HU therapy treatment in all the studies that

used the incidence of VOC as an indicator.[7-24] Hospitalization and blood transfusion rates have also significantly reduced after HU therapy. Ten studies reported the frequency of hospitalization, and all reported a significant reduction in hospitalization.[7,8,12-15,18,20,22,23] A study from Odisha reported a reduction in the duration of the hospitalization.[17] Twelve studies assessed changes in the incidence of blood transfusion and reported the reduction of blood transfusion needs after HU therapy.[7,10,12,13,15,17-20,22,23] However, this reduction is not significant in one study.[14]

Haematological parameters were also compared similarly. Across the studies, there was an increase in the levels of Hb, Hb F, MCV, MCH and MCHC, whereas the levels of Hb S, WBC, platelets, etc., are reduced after treatment with HU. Fourteen studies have shown that these differences are significant.[7-10,12-20,22] However, there are variations in the usage of these parameters, and all studies have not used all parameters. Twelve studies reported a significant increase in Hb F levels after HU therapy.[7-10,13-20] Thirteen studies reported improvement in Hb level [7-10,12-20] and reduction in the prevalence of anaemia.[22]

TABLE 1: CHARACTERISTICS AND INTERVENTION OUTCOMES OF THE SELECTED STUDIES

SR. NO.	DISTRICT/ STATE	TARGET GROUP/ SAMPLE SIZE (N)	STUDY DESIGN	IMPACT	REFERENCE
1.	Sambalpur/ Odisha	All ages n=104	Prospective open-label observational study	• Reduction in the number of vaso-occlusive crises (VOC) • Reduction in blood transfusions • Hospitalization rates and length of stay decreased • HbF, mean corpuscular volume (MCV) and mean corpuscular Hb (MCH) increased • HbS, white blood cells (WBC), platelet, total serum bilirubin, absolute neutrophil count (ANC) and lactate dehydrogenase (LDH) decreased	Dehury et al.[7]
2.	Nagpur/ Maharashtra	All ages n=40	Long-term observational study	• VOC, hospitalization, stroke, severe anaemia, and acute chest syndrome decreased • HbF, Hb, MCV, MCH increased	Jain et al.[8]
3.	Sambalpur/ Odisha	Children and adults (3-45 years) n=118	Prospective open-label observational study	• Reduction in number of VOCs • HbF, Hb, MCV, MCH and MCHC increased • HbS, WBC, Platelet, total serum bilirubin decreased	Patel et al.[9]
4.	Brahmapur/ Odisha	Children (5-14 years) n=114	Prospective cohort study	• Reduction in VOC and blood transfusions • HbF, Hb, MCV, MCH and MCHC increased	Barma et al.[10]
5.	Indore/ Madhya Pradesh	Children (5-14 years) n=73	Prospective analytical study	• Improves scholastic performance • Mean school attendance increased • Grades of students improved significantly	Joshi et al.[11]
6.	Indore/ Madhya Pradesh	Children (5-14 years) n=49	Prospective analytical study	• Reduction in VOC, blood transfusions, and hospitalizations • An increase in haemoglobin levels • Platelet, TLC decreased	Joshi et al.[12]
7.	Vadodara/ Gujarat	All Ages n=70	Observational study	• Decrease in VOC • Reduction in blood transfusion • Decrease in hospitalization • Decrease in WBC, TLC and platelet	Despande et al.[13]

SR. NO.	DISTRICT/ STATE	TARGET GROUP/ SAMPLE SIZE (N)	STUDY DESIGN	IMPACT	REFERENCE
8.	Jagdalpur/ Chhattisgarh	All Ages n=24	Prospective observational study	• Decrease in VOC and hospitalization • Increase in Hb, HbF and MCV • No significant change in MCHC • Decrease in WBC	Singh et al. [14]
9.	Mumbai/Maharashtra	Children and adults (5-35 years) n=77	Prospective observational study	• Reduction in VOC, blood transfusion and hospitalization • Reduction in frequency of stroke • Increase in Hb, HbF, MCH, MCV, MCHC • Decrease in Acute chest syndrome • Decrease in Acute WBC and PLT	Italia et al.[15]
10.	Nagpur/ Maharashtra	Children (5-15 years) n=40	Prospective longitudinal study	• No recurrence of acute chest syndrome • Hb and HbF increased • Reduction in acute painful events • Decrease in blood transfusion	Somkuwar et al. [16]
11.	Sambalpur/ Odisha	All Ages n=42	Longitudinal study	• Reduction in the number of VOC • Reduction in blood transfusions. • HbF, MCV and MCH increased. • HbS, WBC, Platelet, total serum bilirubin, ANC and LDH decreased	Patel et al.[17]
12.	Nagpur/ Maharashtra	Children (below 18 years) n=144	Prospective longitudinal study	• Reduction in VOC, acute chest syndrome, sequestration crises. • Hospitalizations and blood transfusions decreased • Reduction in platelet leucocyte count, platelet count, and reticulocyte count • HbF, Hb, MCV increased.	Jain et al.[18]
13.	Cuttack/ Orissa	Adult (≥ 18 years age) n=128	Longitudinal Study	• Reduction in VOC and blood transfusions, • HbF, Hb, MCV and MCH increased. • Hbs, Platelet, total serum bilirubin, TLC and LDH decreased	Sethy, Panda and Jena.[19]
14.	Nagpur/ Maharashtra	Children (5 to 18 years) n=60	Double blind randomized controlled trial	• Reduction in VOC, blood transfusions, and hospitalizations • HbF and Hb, increased. • Decreased WBC, total serum bilirubin, and reticulocyte count	Jain et al.[20]
15.	Odisha/ India	All Ages n=46	Case-control study	• Reduction of pain in the hip joints • Radiological anomalies vanished. • SCD with segmental collapse of the femoral head resulted in pain decrease	Jena and Swain.[19]

Abbreviations: Absolute Neutrophil Count (ANC), Lactate Dehydrogenase (LDH), Mean Corpuscular Hb (MCH), Mean Corpuscular Volume (MCV), Sickle Cell Disease (SCD), Total Leucocyte Count (TLC), Vaso-Occlusive Crisis (VOC), White Blood Cells (WBC).

RECOMMENDATION:

1. HU is cheap, user-friendly, and safe, with remarkable outcomes among Indian SCD patients.
2. The starting dose of HU 10mg/ kg/day is adequate in most cases, and this can be increased gradually to MTD (35 mg/kg/day) whenever required.
3. Regimens having HU alone or in combinations have been shown to reduce the incidence of VOC, hospitalization and blood transfusion.
4. Several haematological parameters have also been improved after HU therapy.
5. HU cannot be recommended during pregnancy. However, it can be used in exceptional cases under medical supervision after the first trimester.
6. SCD patients require lifelong HU therapy. Hence, interventions to promote treatment adherence are essential.

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CHAPTER 6

Iron Overload & Chelation Therapy

Contrast to Thalassaemia destruction of RBC in SCD is intravascular which provides a potential mechanism for iron elimination in SCD through increased excretion of urinary and biliary iron as Hb, hemosiderin, or heme. Blood transfusion plays an important role in the management of patients with SCD and is the main cause of iron overload. A unit of RBCs contains 200 mg of iron. The age of commencing blood transfusion, the rate of blood transfusion, and the nature of the transfusion regime itself all affect the rate and extent of iron overload in SCD.

Iron derived from transfused RBCs initially accumulates in macrophages and later in hepatocytes. In advanced transfusional iron overload, iron deposition has also been reported in Cardiomyocytes. Endocrine disturbances attributable to iron overload are rare in SCD.

The Indian SCD patients are mostly Arab-Indian Haplo type. Predominant clinical problem is vaso-occlusive type while hemolytic phenotype and combination of VOC and hemolytic phenotypes are less common. Study of Pranati Mohanty et al.,[6] from Eastern India showed that only 9.6% of SCD (HbSS) patients had significant iron overload requiring Iron chelation.

ASSESSMENT OF IRON OVERLOAD

Serum Ferritin (SF) is the most frequently used test to estimate iron overload, but has some particular limitations in SCD. Ferritin is disproportionately increased in relation to iron loading for several weeks after a vaso-occlusive sickle crisis. Relationship of SF with total body iron is not linear after 20 units of BT or SF value of 1500-2000 ng/mL. Reverse also happens during monitoring of chelation therapy lowering of iron load is not reflected by SF even at one year .

SERUM FERRITIN

1. First study after 10 transfusion.
2. Ferritin to be measured after each transfusion or monthly.
3. If ferritin trends are not consistent with the clinical circumstance, LIC to be measured.
4. Critical treatment decisions based on ferritin alone should be made with great caution.

VALUE OF LIC MONITORING

1. This reliable non-invasive liver iron measurement is valuable when starting and planning chelation therapy.
2. Measure LIC if SF trend does not fit with clinical picture.
3. If there is no downward trend in SF, LIC estimation may be required for modifying chelation.

OTHER MONITORING OF IRON OVERLOAD IN SCD

1. If a patient presents with a long-standing high SF or high LIC values, it is useful to know whether myocardial iron has accumulated by T2*.
2. Cardiac T2* should be measured in any SCD patient who has had significant liver iron loading (LIC > 20 mg/g) over many years.
3. Monitoring for the consequences of iron overload is also important. This includes annual monitoring of following in severely iron overloaded patients: (LIC > 20mg / g)

a. thyroid function.
b. glucose metabolism.
c. morning cortisol.
d. adrenocorticotropic hormone and sex hormone.

THERAPEUTIC STRATEGIES

Commencement of chelation therapy when

1. SF is > 1000 ng/mL.
2. LIC is > 3.5 mg/g dry weight.
3. Received 10 transfusion or cumulative transfusions of > 120 mL of packed RBCs/kg.
4. If the cardiac T2* is 8 ms or less aggressive chelation is in-

dicated.

5. The regimens to be individually tailored for each patient to respect their lifestyle and to minimise toxicity.
6. If the patient is on regular simple transfusions, the chelation should not be totally stopped.

CHELATING AGENTS

	DEFEROXAMINE	DEFERIPRONE	DEFERASIROX
Route of administration	Parenteral	Oral	Oral
Dose	40-50mg / Kg/d	75-100mg /Kg/d	20-40mg/Kg/d
Administration	Over 10-24 hrs subcutaneously	Three times daily	Diluted in water or fruit juice. Once daily, two divided doses improves tolerance
Use in renal impairment	Can be used	Can be used	Cannot be used
Removal of cardiac iron	Effective when given by continuous intravenous infusion	Most effective	Effective on long time use

ALTERATION OF CHELATION DOSE WITH TRANSFUSION

Transfusion modality	Iron accumulation mg/kg/d	DFO dose to balance input	DFX dose to balance input
Simple transfusion Target < 30% HbS	0.42	40 mg/kg X 5 /wk	20 mg/kg/d
Simple transfusion Target < 50% HbS	0.32	32 mg/kg X 5/wk	16 mg/kg/d
Automated exchange Target 50% HbS	0.057	< 10 mg/kg X 5/wk	10 mg/kg 5/wk

Combination Therapy(DFX + DFP)

1. Ferritin > 2500 ng / ml.
2. very high LIC (>15–20 mg/g).
3. No response after 6-12 months of monotherapy.

DURING TREATMENT, MONITOR

1. Blood pressure.
2. Creatinine.
3. Creatinine clearance.
4. Neutrophil and platelet counts.
5. Urine protein/creatinine at every transfusion visit.
6. Liver functions and electrolytes at least every 3 months.
7. Audiogram and eye examinations are done annually, (if on DFO).
8. Stop DFX immediately if there is severe abdominal pain and to contact the centre.
9. Stop DFP immediately and go to the emergency room for a blood test if there is fever.

THERAPY CHANGES

1. Ferritin <2000 ng/mL change combination therapy to single agent.
2. Ferritin < 1000 ng/mL reduce dose of chelating agent.
3. Ferritin < 800 ng/mL reduce dose or stop therapy depending on transfusion status.

CHELATOR TOXICITY

TOXICITY	MANAGEMENT
DFO	
Injection site reaction	1.Make sure that the needle is not intradermal 2. Rotate injection site 3. Lower concentration of drug 4. Add small amount of hydrocortisone 10- 20 mg
Infection	Increased risk for ferrophilic organism like Yersinia
Retinal / Auditory	Stop drug. Annual monitoring
DFP	
Gastrointestinal	Usually resolves within a month or two
Transaminitis	Hold the drug, start at lower dose
Neutropenia	Hold the drug till recovery
Arthropathy	Hold the drug , restart at lower doses
DFX	
Gastrointestinal	1. Lower dose 2. Give in two divided doses 3. New formulation
Renal	1. Monitor urine protein/Creatinine at each transfusion visit 2. In case of impaired function stop drug, restart at lower dose
Transaminitis	Monitor LFT every 3 months

RECOMMENDATION:

1. Sickle Cell patients with Arab-Indian haplo type are the main category seen in India. The predominant phenotype is vaso-occlusive and thus iron overload requiring Chelation is not required in most of the cases.
2. Iron overload is possible in SCD and should be considered if anyone of the criteria is fulfilled - SF is > 1000 ng/mL , LIC is > 3.5 mg/g dry weight, received 10 transfusion or cumulative transfusions of > 120 mL of packed RBCs/kg or if the cardiac T2* is 8 ms or less aggressive chelation is indicated.
3. Deferasirox at the dose 20 to 40mg/kg/day is the preferred agent.
4. Combination of Deferasirox and Deferiprone may be considered if the serum ferritin level is not controlled with DFX alone or there is a need of potentiating the iron chelation due to the iron overload in various organs.

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CHAPTER 7

Vaso-Occlusive Crisis Acute Pain

Acute painful sickle cell episodes occur unpredictably, often without clear precipitating factors. Their frequency may vary from less than one episode a year to severe pain at least once a week. Pain can fluctuate in both intensity and duration, and may be at times excruciating. Nearly all individuals affected by SCD will experience a VOC during their lifetime.[7] The first Vaso-occlusive Crisis (VOC) may occur as early as six months of age, often presenting as dactylitis, but thereafter VOCs occur with variable frequency.[8,9,10] VOCs and their accompanying pain most commonly occur in the extremities, chest, and back. When they occur in other sites, they can be confused with, or can be the prodromal stage of, other acute complications (e.g., head (stroke), flank (papillary necrosis), and abdomen (hepatic or splenic sequestration, constipation from opioid toxicity, or another hepatobiliary complication). The etiology of the pain must be determined in order to rule out potential causes of pain other than an uncomplicated VOC, such as ACS, pneumonia, or other abdominal complications. VOC can still occur in the presence of other complications. There are no tests to rule in or to rule out a VOC; there are only tests that potentially rule out other causes of pain. Persons with the genotypes HbSS or HbSβ0 -thalassemia are likely to experience more frequent VOCs. Persons with HbAS (commonly referred to as sickle cell trait) do not experience typical VOCs. Individuals with more than three hospitalizations for a VOC in a year are at an increased risk of early death.[7,9,11-13] The pathophysiology of Vaso occlusive crisis is complex, it usually results into ischaemic damage of tissue. Recurrent episodes may lead to irreversible damage to organs. The majority of painful episodes are managed at home, with patients usually seeking hospital care only if the pain is uncontrolled or they have no access to analgesia. Goal of efficient VOC management is not only faster pain control but prevent tissue damage from ischaemic injury.

ACUTE PAIN MANAGEMENT

Early, aggressive, adequate treatment of pain is an essential component of the management of SCD.[14 -17] Pain management must be guided by patient report of pain severity. No biomarkers or imaging studies can validate pain or assess its severity.[2]

Key features of acute pain management include the following:

- **Rapid Evaluation at Emergency Department.**
- **Prompt pain relief with Analgesia.**
- **Other considerations –Adjuvant Therapies.**

RAPID EVALUATION AT EMERGENCY DEPARTMENT

For those who present to the emergency department or day hospital, there should be rapid assessment of pain and SCD comorbidities that may require additional treatment.

Treat an acute painful sickle cell episode as an acute medical emergency. Rapid (within 1 hour of ED arrival) assessment and administration of analgesia with frequent reassessments (every 30 to 60 minutes) are to be done to optimize pain control.[1]

On arrival at emergency department along with pain assessment it is important to note down vitals .[5]

- Blood pressure.
- Oxygen saturation on air (if oxygen saturation is 95% or below, offer oxygen therapy).
- Pulse rate.
- Respiratory rate.
- Temperature.

Pain Assessment at Presentation: Aim is to determine whether their pain is being caused by an acute painful sickle cell vaso occlusive episode or whether an alternative diagnosis is possible, particularly if pain is reported as atypical by the patient.Use an age-appropriate pain scoring tool. Physicians should reassess pain frequently and adjust treatment to provide relief.

Figures 1 to 3 are examples of assessment instruments.

Figure 1 is a unidimensional "Faces' Pain" intensity scale.[18,19]

Figures 2 and 3 show a visual analogue scale (VAS) [20] and multidimensional scales for either chronic or acute pain assessment.

Diaries are also useful for assessment of pain at home. [21]

FIG1: WONG-BAKER FACES PAIN RATING SCALE [18,19]

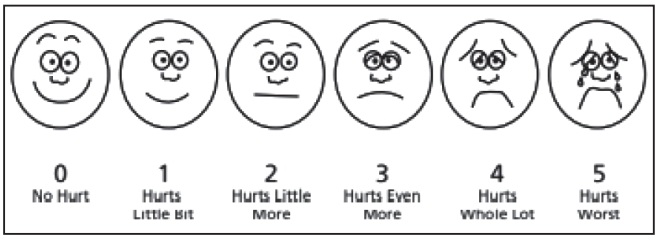


FIG 2: MEMORIAL PAIN ASSESSMENT CARD [20]

For adolescents and adults, the card can be folded along the broken line so that each measure is presented separately in the numbered order.

Throughout an acute painful sickle cell episode, regard the patient (and/or their carer) as an expert in their condition, listen to their views and discuss with them:

- The planned treatment regimen for the episode.
- Treatment received during previous episodes.
- Any concerns they may have about the current episode.
- Any psychological and/or social support they may need.

Patients should undergo a thorough history and physical examination to determine whether an illness might have precipitated the pain, so that the cause and symptom can be treated simultaneously. Patients should be seen immediately by a physician if they experience severe abdominal pain, recurrent vomiting, respiratory symptoms, neurologic signs of paresis or paralysis, acute joint swelling, priapism, or abrupt fall in haemoglobin. Superimposition of acute pain on chronic pain may confound assessment and treatment.

PROMPT PAIN RELIEF WITH ANALGESIA

Analgesia should be provided rapidly and its efficacy as-

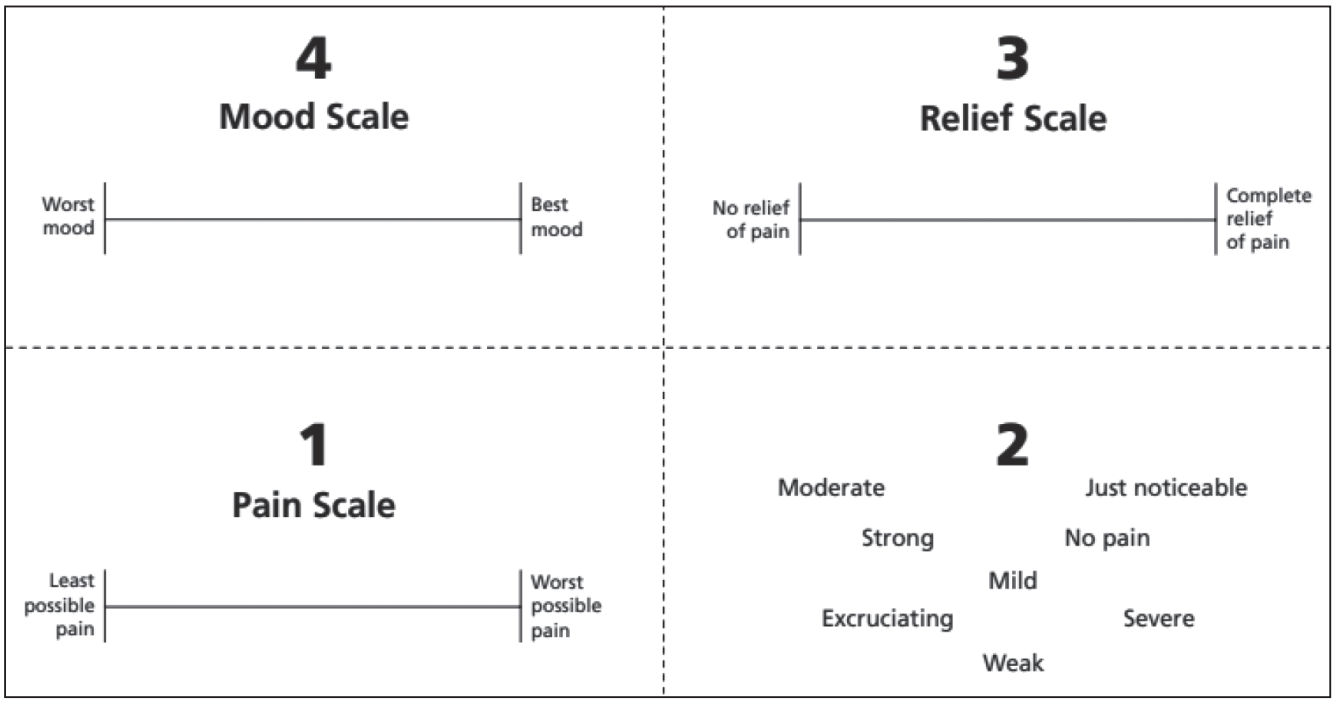
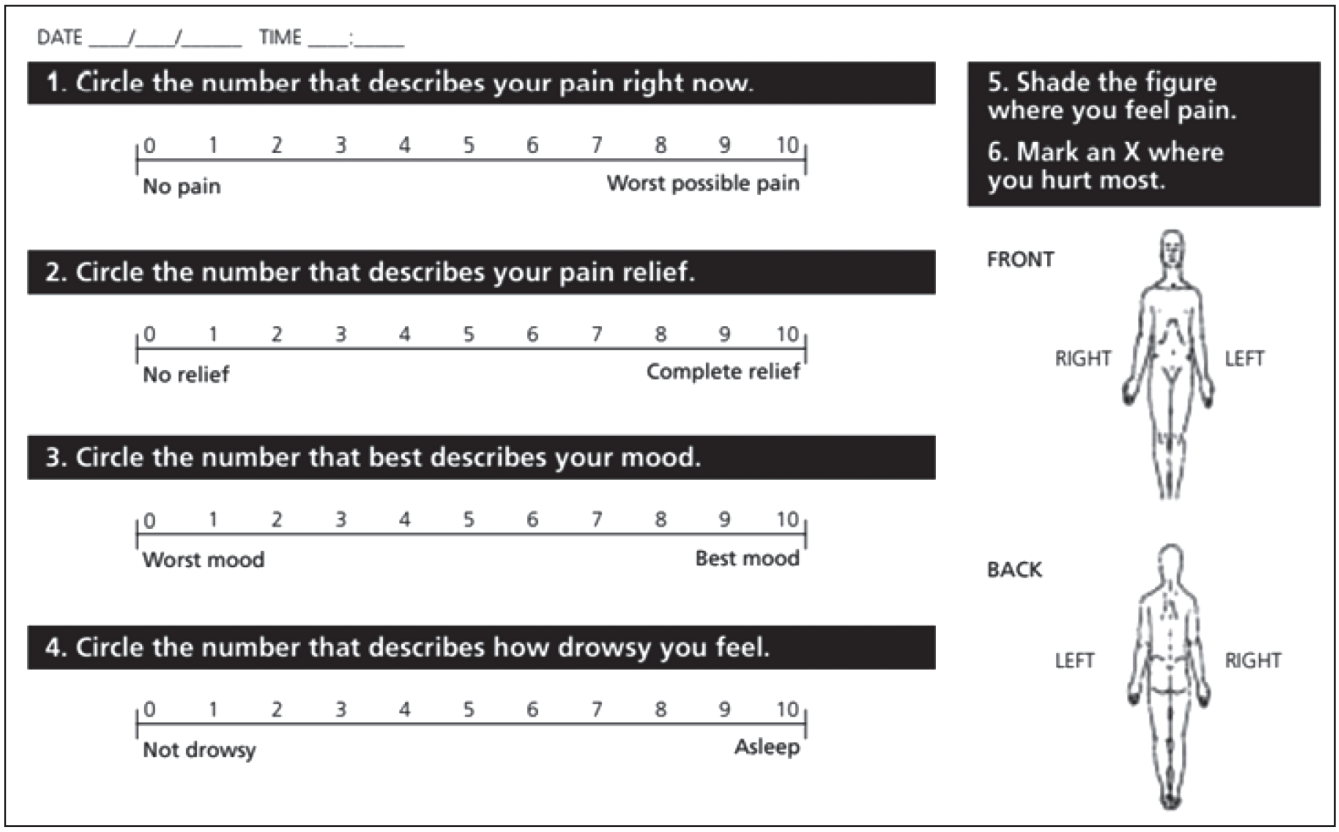


FIG 3: MULTIDIMENSIONAL ASSESSMENT OF ACUTE PAIN [20]



sessed frequently. As noted in the 2020 American Society of Hematology (ASH) guideline, standardized protocols are useful to ensure rapid analgesia for all individuals with sickle cell disease.[17] Attention should be paid to hydration status, venous thromboembolism prophylaxis, renal and hepatic function, and potential opioid side effects.[5]

General Principle for Primary Analgesia: As suggested in NICE clinical guideline 143 Developed by the Centre for Clinical Practice at NICE NHS 2012 individualised assessment at presentation should be done :

Ask about and take into account any analgesia taken by the patient for the current episode before presentation.

Ensure that the drug, dose and administration route are suitable for the severity of the pain and the age of the patient.

Refer to the patient's individual care plan if available.

Offer a bolus dose of a strong opioid by a suitable administration route, in accordance with locally agreed protocols for managing acute painful sickle cell episodes, to all patients presenting with severe pain.

All patients presenting with moderate pain who have already had some analgesia before presentation, consider a weak opioid as an alternative to a strong opioid for patients presenting with moderate pain who have not yet had any analgesia.

Offer all patients regular paracetamol and NSAIDs (non-steroidal anti-inflammatory drugs) by a suitable administration route, in addition to an opioid, unless contraindicated.[22]

The use of NSAIDs should be avoided during pregnancy, unless the potential benefits outweigh the risks. NSAIDs should be avoided for treating an acute painful sickle cell episode in women in the third trimester.[22]

Do not offer pethidine for treating pain in an acute painful sickle cell episode.[2]

PHARMACOLOGICAL MANAGEMENT OF SICKLE PAIN

Analgesics are the foundation for the management of sickle cell pain, and their use should be tailored to the individual patient. Sedatives and anxiolytics alone should not be used to manage pain, because they can mask the behavioural response to pain without providing analgesia. Management of pain associated with SCD consists of the use of opioids, (NSAIDs) and adjuvant medications.[23,24]

NON-OPIOID PHARMACOLOGICAL AGENTS

ROLE OF NSAIDs

A 2020 guideline from the American Society of Hematology (ASH) suggests a short course (five to seven days) of a NSAID in addition to opioids for acute pain management in children and adults with SCD.[1] As stated in the guideline, this is a conditional recommendation based on very low certainty in the evidence for benefit.

Management of mild-to-moderate pain should include NSAIDs or acetaminophen, unless there is a contraindication; these are non-sedating, so patient activities can continue. If mild-to-moderate pain persists, an opioid can be added.[34]

The potential benefits of NSAID use in acute pain in SCD are low to moderate and include improved pain control, reduced opioid utilization, and decreased length of stay.[35,36,37]

The potential risks associated with NSAID use in acute SCD pain include nephrotoxicity, gastrointestinal disorders, and bleeding.[38] Patients specifically at increased risk of renal toxicity need to be identified before using NSAIDS. comorbidities (e.g.peptic ulcer disease, renal dysfunction, full-dose anticoagulation) are a significant risk factor.

PARACETAMOL[38]

It exerts analgesic and antipyretic but not anti-inflammatory effects. Indeed, it does not inhibit peripheral PGs and therefore appears to have a safer profile than NSAIDs. Moreover, there is considerable evidence of an additional central analgesic effect by inhibition of the liquoral PG synthesis, the nociceptive signal transmission in the spinal cord, and the activation of descending serotonergic pathways.[39] It can be administered by different routes, included IV preparations, providing a more rapid onset of analgesia than the oral route.[68]

- Score 1–4 (MILD Pain) Paracetamol 20 mg/kg/6 hrs (the first dose can be 40 mg/kg/6 hours).
- Score 5–7 (Moderate Pain) Paracetamol 20 mg/kg /6 hrs (the first dose can be 40 mg/kg/6 hours) associated with oral or parenteral tramadol (50–100 mg/6 hours).
- Score 8–10 (Severe Pain) Paracetamol 20 mg/kg/6 hrs (the first dose can be 40 mg/Kg/6 hours) associated with oral morphine (5–10 mg/6 hours) or oxycodone (5–10 mg/6 hours). In case of pain emergency, the IV route should be preferred.

In patients at risk of ACS and/or unsuitable for strong opioids, morphine or oxycodone should be replaced with ketorolac eventually associated with tramadol.

IBUPROFEN[38]

In patients unsuitable for Paracetamol (liver failure), Ibuprofen (10 mg/kg/8 hours) can be used. Should be avoided in patients with borderline renal function or failure and used with caution in patients at high risk of acute chest syndrome.

ACETAMINOPHEN

Doses ranged from 12.5 mg/kg/dose IV every 4 hours to 15 mg/kg/dose IV every 6 hours.

IV acetaminophen reduces pain from a VOC in children with sickle cell disease. Clinically, acetaminophen reduces opioid requirements and opioid-related adverse effects.

ASPIRIN

It is avoided due to a risk of Reye's syndrome.[6]

TRAMADOL[41]

It is an atypical opioid, has particular pharmacological characteristics. It acts on mu-receptors and potentiates the mono-aminergic system acting on the re-uptake of monoaminergic mediators at the level of the inhibitory pain pathways.[43] Tramadol has a better safety profile than the major opioids particularly since it causes less respiratory depression.[44] The co-administration of tramadol and ketorolac has been reported to be a valid balanced analgesia in acute pain syndromes (e.g. post-operative pain, trauma).[42] A combination of ketorolac 0.86 mg/kg/day, tramadol 0.3 mg/kg/hr and metoclopramide 0.57 mg/kg/day can be continuously infused for a maximum of 72 hours.

Oral or parenteral tramadol alone or in combination with Paracetamol (50–100 mg/6 hours) can be given.

REGIONAL ANAESTHESIA

Epidural or peripheral nerve catheter-delivered analgesia for abdominal, hip, or leg pain.

The procedure needs to be technically feasible based on the anatomical location of the pain.

A thorough explanation of the procedure as well as risks, benefits, and alternative options should be provided to patients and families before the procedure.

The recommendation assumes administration of the procedure in a centre that has appropriate resources and expertise.

Data in the direct evidence included (1) reduced opioid utilization [45] and [2] reduced pain.[45,46] Data for outcomes in the indirect evidence included the following:[1] pain: improved pain control compared with opioids in post-operative pain,[49] improved pain control compared with other methods in labor pain,[48] and improved pain control in hip fracture[47]; (2) reduced opioid utilization: reduced supplemental analgesia in hip fracture;[47] and [3] satisfaction with care: a higher proportion of women with labor pain rated their satisfaction with pain relief as excellent or very good.[48]

OPIOIDS

VOC with only severe pain should be treated with opioids (dose as described in figure 4, tables 1-2), with or without NSAIDs and adjuvant medications.[6]

The specific defined terms for opioid administration used are as follows:[1]

Basal: Continuous IV opioid infusion.

On-demand dosing: Opioid administered at an interval that relies on patients declaring their own need. Opioid can be administered via a patient-controlled IV analgesia pump or via an as-needed order for intermittent nausea administered drug.

Scheduled intermittent dosing: opioid administered on a timed schedule that does not rely on the patient asking for the drug.

FIG 4: TABLE 1

	Usual Starting Dose for Moderate-to-Severe Pain	
Medication	**Oral**	**Parenteral**
Short-acting opioid agonists[2]		
Morphine[3] (MSIR)	0.3 mg/kg every 3-4 h	0.1-0.15 mg/kg every 2-4 h
Hydromorphone[3] (Dilaudid)	0.06-0.08 mg/kg every 3-4 h	0.015-0.020 mg/kg every 3-4 h
Meperidine[4] (Demerol)	not recommended (1.1-1.75 mg/kg every 3-4 h only if deemed to be necessary after evaluation).	not recommended (0.75-1.0 mg/kg, 1.1-1.75 mg/kg every 3-4 h only if deemed to be necessary after evaluation).

Usual Starting Doses of Opioid Analgesics in Opioid-Naive Adults and Children ≤ 50 kg Body Weight. [1]

Caution 1: Doses listed for patients with body weight less than 50 kg cannot be used as initial starting doses for babies younger than 6 months of age.

Caution 2: Recommended doses do not apply to patient with renal or hepatic insufficiency, or other conditions affecting drug metabolism and kinetics.

Caution 3: For morphine, hydromorphone and oxymorphone, rectal administration is an alternate route for patients unable to take oral medications. Equianalgesic doses may differ from oral and parenteral doses because of pharmacokinetic differences.

Caution 4: Chronic administration of meperidine may result in central nervous system stimulation, including agitation, irritability, nervousness, tremors, twitches myoclo-

nus, or seizures, due to accumulation of the toxic metabolite normeperidine. The risk is much greater for patients with renal or hepatic impairment.

Caution 5: Addiction to opoids is a concern and should be kept in mind. Every effort is to be made to avoid this important complication.

a) It should be given only in severe cases.
b) It should be available only in the hospital set-up.
c) After monitoring by the doctor this should be stopped.
d) Every effort should be made to use alternative analgesic once the pain has been reduced by Morphine.

FIG 4: TABLE 2

	Usual Starting Dose for Moderate-to-Severe Pain	
Medication	**Oral**	**Parenteral**
Short-acting opioid agonists[2]		
Morphine[3] (MSIR)	10-30 mg every 3-4 h	5-10 mg every 2-4 h
Hydromorphone[3] (Dilaudid)	7.5 mg every 3-4 h	1.5 mg every 3-4 h
Codeine[4]	15-60 mg every 3-6 h	
Meperidine (Demerol)[5]	not recommended (50 -150 mg every 3-4 h only if deemed to be necessary after evaluation).	not recommended (50-150 mg every 3 h only if deemed to be necessary after evaluation).
Oxymorphone[3] (Numorphone)	not available	1-1.5 mg every 6 h or 0.5 mg IV and cautiously titrate upward
Oxycodone (Roxicodone, OXYIR)	10 mg every 4-6 h	not available

Usual Starting Doses of Opioid Analgesics in Opioid-Naive Adults and Children ≥ 50 kg Body Weight.[1]

Caution 1: Recommended doses do not apply to adult patients with body weight less than 50 kg. For recommended starting doses for children and adults less than 50 kg body weight, see table 1.

Caution 2: Recommended doses do not apply to patient with renal or hepatic insufficiency, or other conditions affecting drug metabolism and kinetics.

Caution 3: For morphine, hydromorphone, and oxymorphone, rectal administration is an alternate route for patients unable to take oral medications. Equianalgesic doses may differ from oral and parenteral doses because of pharmacokinetic differences.

Caution 4: Codeine doses higher than 65 mg often are not appropriate because of diminishing incremental analgesia with increasing doses but continually increasing nausea, constipation, and other side effects.

Caution 5: Chronic administration of meperidine may result in central nervous system stimulation, including agitation, irritability, nervousness, tremors, twitches, myoclonus, or seizures, due to accumulation of the toxic metabolite normeperidine. The risk is much greater for patients with renal or hepatic impairment.

Intravenous Opioids is preferred; subcutaneous or intranasal administration can be used for those with difficult intravenous access.

SIDE EFFECTS OF OPIOIDS [6]

Sedation: Usually precedes one of the most feared side effects of opioids, respiratory depression. Fortunately, tolerance to this side effect develops faster than to the analgesic action; nevertheless, nurses should monitor sedation levels when patients are at risk. If sedation persists after prompt intervention, then pulse oximetry, apnea monitors, and blood gas levels may be needed.

Nausea and vomiting: It can be treated with antiemetic such as prochlorparazine, metochlorpropamide, or hydroxyzine.

Pruritus: It can be treated with hydroxyzine or with diphenhydramine; smaller doses given more frequently may be more effective, causing less sedation than larger doses administered less often. Patients should not be considered allergic to an opioid only on the basis of itching.

Constipation: If opioids are prescribed for home use, patients should also take stool softeners daily to prevent constipation.

TOLERANCE, PHYSICAL DEPENDENCE, ADDICTION, AND PSEUDOADDICTION [6]

A major barrier to effective management of sickle cell pain is a lack of understanding of opioid tolerance, physical dependence, and addiction. Tolerance and physical dependence are expected pharmacologic consequences of long-term opioid use and should not be confused with addiction.

Tolerance is a physiologic response to the exogenous administration of opioids, and the first sign is decreased duration of medication action. When tolerance develops, larger

doses or shorter intervals between doses may be needed to achieve the same analgesic effect.

Physical dependence also is a physiologic response to the exogenous administration of opioids. It requires no treatment unless withdrawal symptoms—such as dysphoria, nasal congestion, diarrhea, nausea, vomiting, sweating, and seizures—occur or are anticipated. The risk varies among individuals, but when opioids are given for more than 5 to 7 days, doses definitely should be tapered to avoid physiologic symptoms of withdrawal.

Addiction is a not physical dependence but, rather, a psychologic dependence. Addiction is a complex phenomenon with genetic, psychologic, and social roots. The use of opioids for acute pain relief is not addiction, regardless of the dose or duration of time opioids are taken. Patients with SCD do not appear to be more likely than others to develop addiction. The denial of opioids to patients with SCD due to fear of addiction is unwarranted and can lead to inadequate treatment.

Pseudo addiction[31] applies to patients who receive inadequate doses of opioids or whose doses are not tapered, and therefore they develop characteristics that resemble opioid addiction.

KETAMINE AS ADJUVANT TO OPIOID FOR ACUTE PAIN

Ketamine may be appropriate in individuals with severe pain not responsive to standard opioid analgesics, as suggested in the 2020 American Society of Hematology (ASH) guideline.[1] It is also indicated in individuals with hyperalgesia syndrome. Some institutional protocols include ketamine for initial pain management in the emergency department. Individual pain protocols embedded in the electronic medical record allows inclusion of ketamine in the initial pain plan for individuals whose pain is less responsive to opioids and/or when ketamine is preferred by the patient and providers.

Ketamine is not an opioid. It prevents glutamate activation of the N-methyl-D-aspartate (NMDA) receptor, which may mitigate opioid tolerance. Its analgesic benefits are seen in low, sub-anaesthetic doses. It can be used in the emergency department intranasally at 0.25 mg/kg to a maximum of 1 mg/kg per dose. Continuous intravenous infusion has been reported to be safe and effective in SCD. at approximately 3 to 5 mcg/kg/min (0.3 mg/kg/hour with a maximum of 1 mg/kg per hour.[32,33] However, due to potential renal toxicity, the current recommendation is that ketorolac should not be used for longer than 5 days in a month.[34]

Ketamine is also noted to have an antidepressive effect, which may help in the transition to pain prevention and management of chronic pain.

INTRANASAL FENTANYL

It has been safely used in the initial acute emergency department management of SCD pain, particularly in paediatrics.[25] This agent is rapid-acting, has a short duration of action, and avoids delays associated with obtaining intravenous access. Intranasal fentanyl should be restricted to two doses. A 2014 Cochrane review of the use of intranasal fentanyl found it to be effective for pain control in children >3 years of age without SCD who had moderate to severe pain.[26] For children who weigh ≥10 kg, two doses of 1.5 mcg/kg administered 5 to 10 minutes apart (maximum single dose 100 mcg) have been administered.[25]In contrast to children, there is a lack of high-quality randomized controlled trials in adults with SCD addressing the efficacy and risks of intranasal fentanyl.

NON PHARMACOLOGICAL ADJUVANT THERAPY

Blood transfusion [1,2]

Red blood cell (RBC) transfusion is not a treatment for uncomplicated vaso-occlusive pain without symptomatic anaemia. Importantly, however, vaso-occlusive pain may accompany other SCD complications for which transfusion is indicated. If pain and a complication requiring RBC transfusion are present, pain control and transfusion should be administered concurrently. Patients with acute pain should not be transfused blood/PCV unless there is an additional indication for transfusion.[50]

RESISTANT VOC

Few patients may not respond to the above standard treatment. Reduction of HbS below 30-50% has been proved to be an effective measure in controlling the pain in such situation. This can be achieved bysimple (manual) [74] or automated exchange transfusion (apheresis).

Hydration: Individuals with SCD are frequently hypovolemic during pain episodes; hydration may improve pain control and reduce the likelihood of other complications. Reduced oral intake, increased insensible losses, and reduced urinary-concentrating ability of the kidney (hyposthenuria) may contribute to a negative fluid balance.[51]

Individuals with SCD should pay close attention to adequate hydration. Fluid intake, urinary output, and daily weights should be monitored closely during hospitalization. To avoid over hydration related complications recommendation is to give fluid 60ml/kg /day either IV or Orally.

Oxygen:[1, 2] Do not use oxygen during uncomplicated vaso-occlusive events when the individual's oxygen saturation is normal at room air and there are no pulmonary symptoms. However, it is advisable to monitor closely for these complications and administer oxygen for hypoxemia and/or respiratory indications.

CORTICOSTEROIDS [1]

ICH recommends no use of steroid for treatment of acute pain. There are no studies that addressed some of the prior–defined patient-centred outcomes, including pain, HRQOL, satisfaction with care, and missed days of school or work with use of Steroid in acute pain relief. The risk of re hospitalization increased with steroid exposure.[72]

Psychosocial support: As with any condition that produces chronic pain, SCD pain may be associated with various psychosocial stresses that contribute to depression and social isolation. This may be especially true during transition from paediatric to adult care. Psychosocial support should be appropriate to the individual's needs and may include cognitive-behavioural approaches, relaxation or breathing exercises, yoga, or self-hypnosis.[14,17,60-63]

Massage,[65] Yoga,[63] TENS, Guided imagery/AV relaxation,[66,67] and VR [68] in children or adults with SCD for the management of acute pain.

The potential benefits of acute pain treatment with massage, yoga, TENS, guided AV relaxation/imagery, and VR are small and include improved pain control, pain coping, decreased opioid use, and decreased length of stay. Most patients value additional improved pain outcomes from these nonpharmacological therapies, especially considering that interventions such as yoga and massage likely have lower risks than conventional pharmacological treatments.

Data on all of the existing nonpharmacological therapies lacking (e.g., mindfulness, spirituality, exercise, and cognitive therapy) that may have the potential to reduce acute pain in SCD.

Acupuncture and biofeedback for treatment of acute pain: There is no direct or indirect evidence supporting the idea that biofeedback has benefits for the outcomes of interest.

OTHER ADJUVANT THERAPIES

Other medications recommended during stable condition like Hydroxyurea, folic acid, calcium vitamin D, etc. should be continued during the crisis if no contra-indication.

Treatment for breakthrough pain: It is critical to make additional treatment available for breakthrough pain (defined as transitory pain that occurs intermittently while the individual is receiving opioid therapy, may last only a few minutes to an hour, and is difficult to distinguish from the persistent pain). The hallmark of breakthrough pain is the swift increase in pain while the individual is being treated with continuous or around-the clock opioid therapy.

All individuals hospitalized with pain episodes should have written orders for breakthrough pain medication to maintain a therapeutic effect when the breakthrough pain occurs. The best approach is to provide immediate access to pain medication without requiring the individual to call the nurse and wait for additional medication. This is most easily achieved using PCA with a demand-dose option.

Neuropathic pain: Neuropathic pain may exacerbate acute pain episodes, and therapies directed at neuropathic pain

should be included if appropriate.

Ongoing assessment – All individuals should be assessed with pain tools and sedation scales to ensure that analgesia is adequate and oversedation does not occur. Haemoglobin oxygen saturation monitoring is also helpful in managing severe painful episodes. Orders should include temporary cessation of analgesia and physician notification if the haemoglobin oxygen saturation level decreases by more than four percentage points from the individual's baseline or if bradypnea occurs. Other potential complications of opioids, including gastrointestinal effects and pruritus, should also be anticipated, and managed appropriately.

COMPREHENSIVE ASSESSMENT FOR CHRONIC PAIN OR FOLLOWUP OF PERSONS WHO HAVE ACUTE PAIN

This type of assessment usually occurs at the end of a painful episode, at office/clinic visits for chronic pain, or between episodes. The objective is treatment planning,[70] which involves the patient, family,[71] and health care team. Assessment is multidimensional and should include physiologic, sensory, affective, cognitive, behavioural, and socio-cultural factors.[2]

ALGORITHM OF PAIN MANAGEMENT

FIG 4:[6]

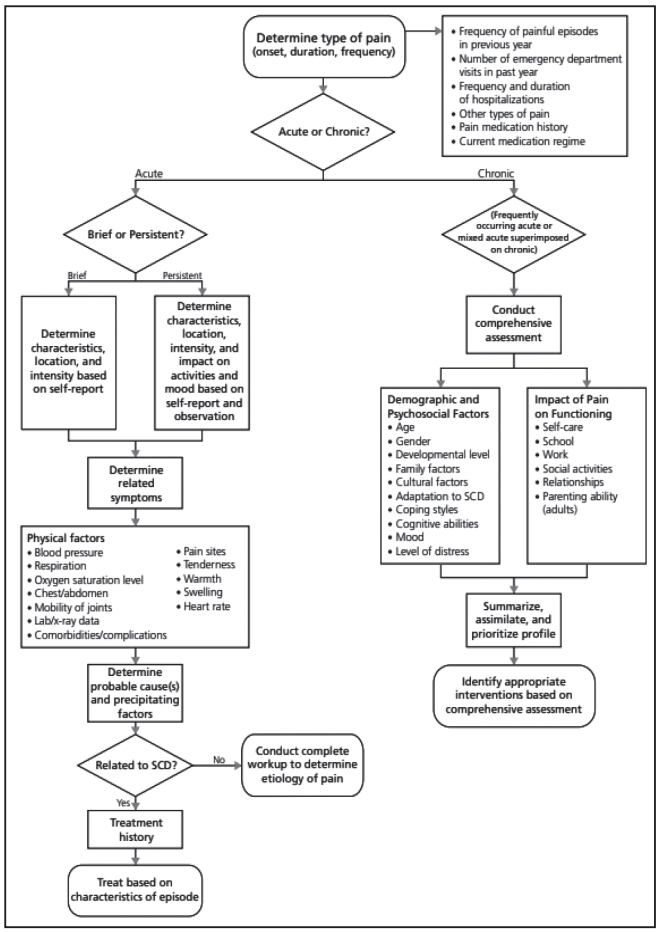
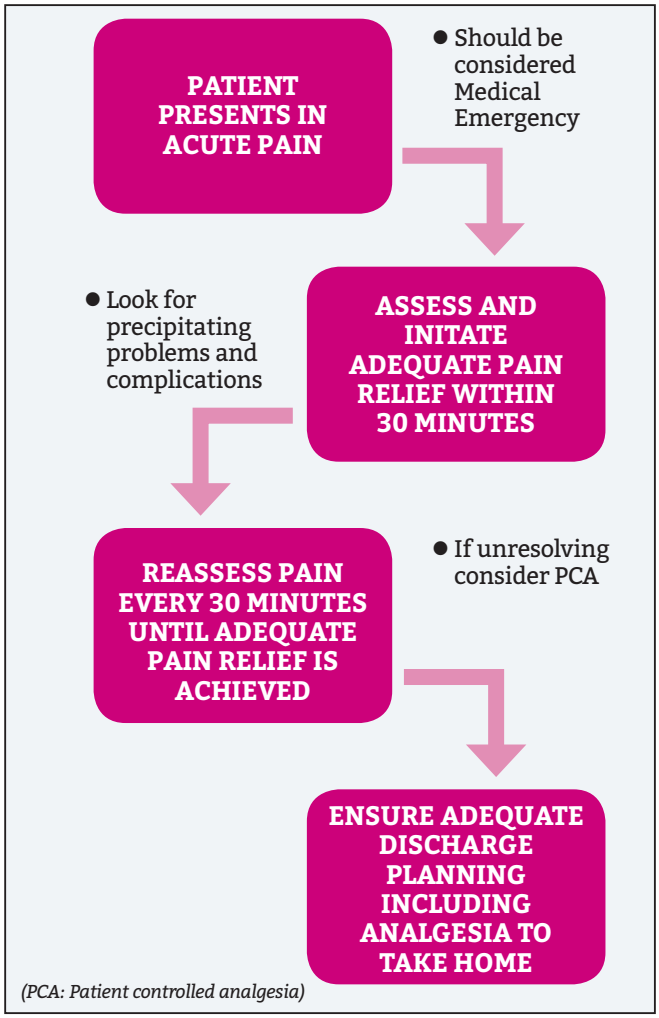


FIG 5:[73]



(PCA: Patient controlled analgesia)

RECOMMENDATIONS:

1. VOC pain in SCD should be controlled aggressively with adequate analgesics like Tramadol, Paracetamol, NSAIDs an, Diclofenac (if no contra-indication) regional Anaesthesia depending on case to case basis.
2. Opoids and buprenorphin patch should be used in severe cases not responding to conventional analgesic with precautions to prevent addiction as mentioned earlier.
3. Other adjuvant therapies like management of fluid, electrolyte, oxygen saturation may be helpful.
4. The medications/adjuvant interventions recommended during stable condition should be continued.
5. Use of steroids during VOC stage may be detrimental and not to be used.
6. Reduction of HbS level below 30-50% by exchange transfusion (simple/red cell apheresis) could be an effective modality in reducing pain in resistant / recurrent VOC.

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CHAPTER 8

Management Of Complications

A. VASO-OCCLUSIVE CRISIS

- Precipitating factors for acute pain full episodes are exercise, infection, dehydration, psychological stress, low fetal Hb.
- HbS polymerization causes change in shape and rheology of RBCs resulting in initiation of inflammatory process involving the endothelium, activation of platelets and leuocytes. Hemolysis also further augments the inflammatory process.
- The blockage in vessels due to HbS polymerization and inflammation leads to pain crises and swelling. Recurrent episodes of chronic inflammation and VOC result in tissue infarction and ultimately end organ damage.
- The underlying pathologic cause is bone marrow ischemia, sometimes leading to frank infarction with acute inflammatory infiltrate.
- Lumbosacral spine and juxta-articular areas of joints like knee, shoulder, and elbow are most commonly involved.
- Each episode of VOC lasts for 9-14 days, and has four phases.

1. Prodromal phase: May be asymptomatic, or may have mild symptoms like numbness, paresthesias.
2. Initial phase: Patients experience peak pain severity.
3. Established phase: Pain severity is sustained. Joint effusion and swelling may be present.
4. Resolving phase: Pain severity decreases, swelling reduces.

- The treatment consists of medication for pain relief, rehydration and reassurance. Resolution is usually complete. The treatment should start in prodromal phase for best results.

B. SEQUESTRATION CRISIS

- Sudden onset trapping of large amount of RBCs in the spleen (rarely liver) followed by rapid and massive enlargement of the spleen constitutes the acute sequestration crisis.
- Manifestations include weakness, dyspnea with splenomegaly, severe anaemia and shock. The hematocrit can reduce to half the patient's usual value within few hours.
- It is characterized by brisk reticulocytosis to 20–30%, with increased nucleated RBCs and moderate to severe thrombocytopenia.
- Usually affects children aged between 3 months and 10 years of age, but can rarely present in adults with persisting splenict issue as well.
- Blood transfusion is indicated in emergency. The pooled blood may return back to the circulation once the crisis subsides, which might result in Hb levels exceeding the calculated levels. Hence caution must be exercised while transfusing blood.
- Sequestration crisis may recur within four months of initial episode. To eliminate recurrences, elective splenectomy after a second episode is recommended. Immunization and prophylactic penicillin for 3 years as a protective measure against capsulated organisms is recommended following splenectomy.

C. APLASTIC CRISIS

- Temporary cessation of bone marrow function, affecting red cell precursors predominantly, due to inter-current viral (most commonly Parvovirus B19) or bacterial infections constitutes aplastic crisis.
- Affected patients present with severe anaemia, but without compensatory reticulocytosis.
- A patient suffering from SCD who presents with reticulocytopenia should be assumed to have parvovirus B19 infection until proven otherwise. It occurs in epidemics, mostly affecting children below 15 years ofage.
- Management primarily includes blood transfusion therapy.
- Recovery phase is marked by daily gradual increase in the reticulocyte count, hence daily monitoring of reticulocyte count should be done.

ACUTE CLINICAL COMPLICATIONS OF SCD AND THEIR MANAGEMENT

	MANIFESTATIONS	TREATMENT
Painful events	• Hand and foot syndrome – involving small joints of hands and feet. • Disappears when bone marrow from small bones of hands and feet stop erythropoietic activity. • Pain and swelling in ribs • Femoral head, humerus and upper part of tibia due to avascular necrosis. • Severe abdominal pain, vomiting, abdominal distension, diminished bowel sounds.	• Hydration • Analgesia • Monitoring response to analgesics • Reassurance
	• Priapism- persistent pain full penile erection; occurs around 4 am during sleep or soon after waking. Lasts for few minutes to several hours.	•If pain, engorgement persists for 24–48 hours- blood transfusion. •Prevention- oral stilbestrol 5 mg daily, gradually tapered and omitted over a period of 2 months.
Infection	• Bacteremia/sepsis, meningitis, osteomyelitis, pneumonia • Clinical features-seriously ill appearance, hypotension, temperature>40°C, total WB Ccount >30000/cm2 or <5000/cm2 and platelet count<1lac/cm2	•Admission for assessment& intravenous antibiotics •Surgical intervention if needed •Prophylaxis with oral penicillin, erythromycin up to 5 years of age and pneumococcal vaccinationis advised.
Anaemia	• Chronic hemolysis due to HbSS • Splenic sequestration • Transient aplastic crisis • Transfusion reaction • Nutritional deficiencies, worm infestation, etc	•Blood transfusion •Multivitamins, calcium and Vitamin D supplements, anti-helminthics, dietary changes • Zinc supplements
Organ damage	• Stroke • Splenicinfarction • Renalpapillary necrosis • Priapism	•Hydration •Blood transfusion
	Acute chest syndrome	• Broad spectrum antibiotics • Oxygen therapy • Exchange transfusion is indicated if hematocrit is high.

CHRONIC COMPLICATIONS OF SCD AND MANAGEMENT

	MANIFESTATIONS	TREATMENT
Heart/Lungs	• Restrictive lung disease • Elevated tricuspid jet velocity • Pulmonary hypertension • Restrictive cardiomyopathy • Left ventricular hypertrophy	• Bronchodilators • Hydroxycarbamide • Blood transfusion • Cardio-Pulmonary consultation
Brain	• Stroke (Ischaemic/hemorrhagic) • Silent infarction • Neurological decline	• Blood transfusion • Hydroxycarbamide

	MANIFESTATIONS	TREATMENT
Liver Kidney	• Jaundice • Cholelithiasis • Acute renal injury with deterioration in renal function • Deterioration of renal function • Reduced concentrating ability • Proteinurea • Progressive renal failure	• Ursodeoxycholic acid • Cholecystectomy • Hepatologist consultation • Dialysis/nephrologist consultation • ACE inhibitor • Angiotensin receptor blockers
Spleen	• Recurrent sequestration crisis • Splenic abscesses	• Splenectomy
	• Hypersplenism – RBC sequestration with splenomegaly, marked anaemia, growth retardation • Infarction	• Blood transfusion • Splenectomy if no resolution in 6 months
Bones/skin	• Avascularnecrosis • Leg ulcers around malleoli/shin of tibia	• Physical therapy • Cord decompression • Woundcare, Zinc supplementation • Surgery • Orthopaedic consultation
Eyes	• Retinopathy (proliferative and non-proliferative) • Vitreous haemorrhage • Retinal detachment	• Laser therapy • Ophthalmology review
Penis	• Impotence • Infertility	• Surgery (if needed) • Urologist consultation
Somatic and sexual growth retardation	• Age of menarche delayed by 2.5 years.	• Zinc supplementation may help. • Endocrinologist consultation
Cognitive and psychological complication	• Cerebral infarcts (silent/overt) • Decreased quality of life	• Ongoing cognitive and school performance assessment. • Counselling • Neuropsychology or neurology consultation

- **FEVER MANAGEMENT**

❖ **Temperature≥101.3°F (38.5°C) and who do not appear ill**

- Thorough history and physical examination, CBC with differential count, reticulocyte count, blood culture, andurine culture when urinary tract infection is suspected.
- Empiric parenteral antibiotics that provide coverage against *Streptococcus pneumonia* and gram-negative enteric organisms to be initiated. Subsequent outpatient management using an oral antibiotic is feasible.

❖ **Temperature ≥103.1 °F (39.5 °C) and who appear ill**

- Hospitalization for close observation.
- Intravenous antibiotic therapy.

❖ **Febrile illness is accompanied by shortness of breath, tachypnea, cough, and/or rales**

- Manage as per aforementioned recommendations.
- Chest X-ray to investigate for ACS.

- **Acute Splenic Sequestration**
- Assess for features of shock, immediately provide IV fluid resuscitation.
- Blood transfusion must be considered for people who have acute splenic sequestration and severe anaemia to raise the haemoglobin to a stable level.
- Consider splenectomy in people with recurrent acute splenic sequestration or symptomatic hypersplenism.
- Acute Chest Syndrome.
- Supplemental O_2 therapy for drop in pulse oximetry by

4% over baseline, or values <90%.
- Blood transfusion therapy.
- Empirical antibiotics to be initiated (third generation cephalosporins and macrolide).
- Incentive spirometry and chest physiotherapy as deemed necessary.
- Pain control and fluid management.
- Blood Transfusion: **See the relevant section**

RECOMMENDATIONS:

1. The complications of SCD can be acute (vaso-occlusive crisis, sequestration crisis and aplastic crisis, haemolytic crisis, etc.) and chronic (involving almost all organs).
2. Regular monitoring should be done to detect any chronic complications/organ damage at early stage.
3. Management of specific organ involvement should preferably be multi-disciplinary approach and the interventions are outlined above.
4. Comorbidities like diabetes, hypertension, renal dysfunction and cardio-respiratory illness, etc., can deteriorate the sickle-related organ damage and thus should be managed aggressively.
5. Disease modifying therapy like HU and blood transfusion (wherever indicated, with extended crossmatching should be considered along with the specific treatment.

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CHAPTER 9

Transfusion Support

All the complications of sickle cell disease (SCD) are because of polymerization of HbS.[1] The management of SCD is focused to prevent HbS polymerization and reduce the circulating HbS percentage. Apart from reducing the HbS percentage, transfusion support in these patients has additional benefits like increasing the percentage of red cells with normal oxygen affinity and increasing Hb level with a longer life span of HbAA. [2,3] This may reduce the endogenous reticulocytosis and production of HbS, though the theory has not been demonstrated yet in the literature.[4] Transfusion support in SCD depends on the clinical condition and feasibility and is of three methods as follows:

1. Simple Transfusion (ST).
2. Manual Red Cell Exchange(M-RCE)[autologous whole blood phlebotomy alternating with allogeneic PRBC and fluid infusion].
3. Automated Red Cell Exchange (A-RCE)[removal of autologous RBC with allogeneic PRBC replacement using an apheresis device].

The detailed comparison of the above three methods of transfusion is depicted in Table-1.

SIMPLE TRANSFUSION Vs RCE

Simple transfusion (ST) is indicated with isolated symptomatic anaemia, like parvovirus B19 aplastic crisis, and splenic sequestration. ST may be indicated acutely as a temporary measure until RCE can be performed for conditions like acute stroke, transient ischemic attack, or rapidly progressive or severe acute chest syndrome. Though A-RCE is preferred over M-RCE for targeted reduction of HbS and serum ferritin levels, the difference is not significant and also A-RCE is not significantly associated with increased risk related to the procedure. [6,7]

INDICATION FOR RBC TRANSFUSION [8]

The indication for RBC transfusion in SCD patients can be categorized as acute and chronic.

ACUTE RCE

1. Acute stroke.
2. Rapidly progressive or severe acute chest syndrome (ACS).
3. Multi-organ failure.
4. Fat embolism syndrome.
5. Acute sickle cell hepatic crisis.
6. Acute hepatic sequestration.
7. Pre-operatively in patients with Hb ≥ 10 gm/dl undergoing moderate-risk surgery.

Chronic RCE is indicated as prophylaxis against stroke, silent infarct, recurrent ACS, recurrent painful episodes, and complicated pregnancy.

Patients with SCD frequently require surgery due to obstructive sleep apnea, adenotonsillar hypertrophy, cholelithiasis, splenic sequestration, and avascular necrosis. Pre-operative RCE is recommended to target HbS level <50% in patients with Hb > 9gm/dl and if Hb < 9gm/dl, ST is recommended. Patients having high-risk surgery (e.g. cardiac or neurologic surgery) should have pre-operative RCE aiming for HbS% of <30%.[9] Transfusion recommendation for different surgical risk in different genotype of patients is given below in Table-2. [*For details, please refer to the chapter on "Sickle Cell Disease (SCD) and Surgery"*]

Prophylactic transfusion is recommended at regular intervals at the onset of pregnancy for women with a history of severe SCD-related complications prior to the current pregnancy, or the development of SCD-related complications during the current pregnancy. Still, there are limited studies on transfusion during pregnancy of SCD patients. Hb level > 7gm/dl and HbS level < 50% is recommended.[6] [*For details, please refer to the chapter "Management of SCD in pregnancy"*]

ADVERSE TRANSFUSION REACTIONS

Every transfusion is associated with a risk of transfu-

TABLE-1: COMPARISON OF DIFFERENT METHOD OF TRANSFUSION[2,5]

	SIMPLE TRANSFUSION	MANUAL RCE(M-RCE)	AUTOMATED RCE (A-RCE)
Availability	Easily available	Easily available	Limited
Feasibility	Any hospital	Minimal expertise	Expert and Equipment required
Staff Training	Minimal	Some	Significant
Equipment	Minimal	Minimal	Apheresis machine
Duration	Time consuming	Time consuming	Rapid procedure
Frequency	Short Interval	Intermediate	Long interval
Venous access	Peripheral	Peripheral± Central	Central: High requirement Peripheral: Fixed vein
Reduction in HbS%	Poor control	Intermediate	Targeted therapy
Iron Accumulation	High	Intermediate	Low
Risk of Hyperviscosity	High with high Hb	Less	Less
Indications	Acute anaemia Low risk surgery in HbSβ^0 Thalassemia with Hb <9	Acute stroke Acutely unwell (multi organ failure): Need ICU Support High Risk surgery (cardiac/Neurosurgery)	Acute Stroke Acutely unwell (multi organ failure): Need ICU Support High Risk surgery (cardiac/Neurosurgery)

TABLE-2: TRANSFUSION RECOMMENDATION FOR DIFFERENT SURGICAL RISK

GENOTYPE	HB(G/DL)	SURGICAL RISK	RECOMMENDATION
HbSS/HbS^0 Thalassemia	<9g/dL	Low/Moderate	Simple transfusion/partial exchange/RCE
HbSS/Hbβ^0 Thalassemia	>9g/dL	Low/Moderate	Partial exchange/RCE
HbSC/Hbβ^0/HbSS on Hydroxyurea with elevated HbF without severe phenotype	>9g/dL	Low	No transfusion
HbSC/HbSβ^0 Thalassemia	>9g/dL	Moderate	Partial exchange/RCE
All Genotypes		High	RCE

sion-transmitted infection, haemolytic transfusion reaction, allergy, FNHTR, TRALI, iron overload, etc which is depicted in Table-3.[10] But, the management of DHTR in SCD patients is challenging and the mitigation policy should be considered to reduce the morbidity and mortality associated with transfusion.

Delayed Hemolytic Transfusion Reaction/ Hyperhemolysis:

DHTR is defined as a significant drop in Hb level within 21 days of post-transfusion associated with alloimmunization/haemoglobinuria/reticulocytopenia or reticulocytosis/raised LDH/ accelerated increase in HbS% with concomitant reduction in HbA level and exclusion of other causes. Rapid decline in Hb below the pre-transfusion level and rapid decline of post-transfusion HbA level is defined as Hyperhemolysis. The alloimmunization rate among SCD patients, transfusion with ABO and RhD matched red cell is much higher than the other multi-transfused patients, ranging from 18% to 45% and the findings are similar to the study done from the Eastern part of India having a high prevalence of SCD.[11-14] The cause of alloimmunization is the difference in RBC antigen expression between patient and donor unit, ethnic/ racial difference, immunological response of the patient, immunogenicity of the blood

TABLE-1: COMPARISON OF DIFFERENT METHOD OF TRANSFUSION[2,5]

SN	Type of Transfusion Reaction	Prevalence (per 1,00,000 unit transfusion)	Mitigation strategy
1	Febrile non-hemolytic transfusion reaction (FNHTR)	1000-3000	Leukoreduction
2	Allergic reaction	112.2	Washed PRBC
3	Delayed hemolytic transfusion reaction (DHTR)	40	Rh, Kell phenotype matched compatible unit transfusion
4	Acute hemolytic transfusion reaction (AHTR)	2.5-7.9	Rh, Kell phenotype matched compatible unit transfusion
5	Transfusion related lung injury (TRALI)	0.4-1	Plasma transfusion is more commonly implicated in TRALI. Hence, transfusion ofplasma products from a multiparous female donor is always avoided.
6	Transfusion associated cardiac overload (TACO)	10.9	RCE has less chance of TACO.
7	Septic transfusion reaction	0.03-3.3	More commonly implicated in platelet transfusions. The skin flora of the blood donor is a primary source of bacterial contamination, and needles used for venipuncture may generate a small skin plug. Diversion of the initial blood volume (for example, 10 – 20 mL) reduces bacterial contamination of collected blood.
8	Red cell alloimmunization	50% without matching 5-24% with Rh,K matching 7% with Rh, K, Duffy, Kidd, S	Extended phenotype matched compatible unit transfusion
9	Iron overload		Routine MRI of the liver after 10 units transfusion, Iron chelation therapy
10	Hyperhemolysis transfusion reaction	1-4%	1. Avoid transfusion as much as possible 2. IVIG

group antigen and other risk factors like age and sex of the patient, old age and leukocyte contain of the blood unit.[15] So Red blood cell of choice for transfusion either in ST or RCE is Rh, Kell matched (if possible Kidd, Duffy, and MNS matched), leukoreduced, sickle cell negative, less than 7 days old, and AHG cross matched compatible unit, should be transfused to avoid alloimmunization.[6,8,16] In patients with SCD (all genotypes) with an acute need for transfusion and at high risk for AHTR or with a history of multiple or life-threatening DHTR, immunosuppressive therapy (intravenous immunoglobulin. [IVIg], steroids, and/or rituximab) over no immunosuppressive therapy is recommended.[6]

IMMUNO-HEMATOLOGICAL WORKUP IN A PATIENT OF SCD

1. Blood grouping.
2. Extended red cell antigen phenotype (C, c, E, e, K, k, Fya, Fyb, JKa, JKb, MNS).
3. Antibody screening and Identification (Rule out alloimmunization/ DHTR).

In Pregnancy: At Booking then at 28weeks of gestational age (GA), If antibody is present every monthly up to 28 weeks and then 2 weekly after 28 weeks of GA.

4. DAT/Monospecific DAT (DHTR, Hyperhemolysis: C3d

positive, IgG: Negative)

TRANSFUSION RECOMMENDATIONS

1. Red cell antigenic profile should be performed at the earliest opportunity, optimally before 1st transfusion. It includes minimum Rh (D, C, c, E, e), and Kell. It is preferable to include Duffy, Kidd, and MNS.
2. An extended red cell antigen profile by genotype or serology over only ABO/RhD typing for all patients with SCD.
3. Transfusion should be done only when it is needed and cannot be managed by alternatives. Red cell transfusion if needed should be selected as per the antigen profile as mentioned below.
4. **Red blood cell of choice for transfusion in ST and RCE:** At least Rh, Kell matched, and preferably Duffy, Kidd, and MNS matched donor blood unit, leukoreduced, sickle cell negative, and less than 7 days old, and AHG cross matched compatible unit, should be selected for transfusion.
5. Antibody screening should be included in pre-transfusion testing of previously transfused SCD patients.

RECOMMENDATIONS:

1. Transfusion should be done only when it is needed and cannot be managed by alternatives. Red cell transfusion if needed, should be selected as per the antigen profile mentioned below.
2. Red cell antigenic profile should be performed at the earliest opportunity, optimally before 1st transfusion. It includes minimum Rh (D,C,c,E,e), and Kell. It is preferable to include Duffy, Kidd, and MNS especially if there is already development of allo-antibodies.
3. An extended red cell antigen profile by genotype or serology over only ABO/RhD typing for all patients with SCD.
4. Red blood cell of choice for transfusion in ST and RCE: At least Rh, Kell matched, and preferably Duffy, Kidd, and MNS matched donor blood unit, leuko reduced, sickle cell negative, and less than 7 days old, and AHG cross matched compatible unit, should be selected for transfusion.
5. Antibody screening should be included in pre-transfusion testing of previously transfused SCD patients.
6. The management of post-transfused hemolytic reaction should be done with IVIG, high dose of EPO and other supportive therapy.
7. High risk patients (who have already developed allo-antibodies) who need blood transfusion as life saving procedure should receive prophylactic Rituximab.

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CHAPTER 10

Hematopoietic Cell Transplant & Gene Therapy

Sickle cell disease is the most common inherited haemoglobinopathy worldwide, and is a devastating, life threatening disease with limited therapeutic options to reduce disease severity. Although more than 94% of children with SCD in well-resourced countries now survive until the age of 18 years due to routine newborn screening, penicillin prophylaxis, primary stroke prevention, and hydroxyurea (HU) therapy, chronic complications (that include stroke, sickle lung disease, renal failure, RBC allo-immunization, etc.) severely impact the quality of life (QoL), and mortality is still significant once patients reach adulthood. Majority of patients develop end organ damage due to repeated sickling crisis episodes, which ultimately severely cripple their young adult life. In India, the scenario is even more dismal. Despite the fact that the sickle phenotype prevalent in our country is of milder form as compared to the African counterpart due to high HbF levels, it is estimated that about 20% of children with sickle diseases died by the age of two as reported in one ICMR survey, and 30% children with SCD among the tribal community die before they reach adulthood[1]. Additionally as SCD is particularly prevalent in tribal populations in our country, which comprise the most socioeconomically disadvantaged communities with lack of medical facilities to care for their disease, the estimates for chronic complications for SCD are expected to be very high. Thus it is estimated that unlike in the west, majority of patients of SCD who reach adulthood in our country develop chronic complications, thereby significantly compromising their QoL as well as adding liability to the already burdened health care system of our country. Current treatment options, such as Hydroxyurea and regular transfusion therapy for the disease, only ameliorate the disease severity rather than actually curing it. In light of this, an allogeneic hematopoietic cell transplant (allo-HCT) is the only treatment strategy that is widely available in the country and can actually cure this disease. More recently there is increasing excitement on the prospect of gene therapy becoming a one-time curative procedure for patients with sickle cell disease. There are different strategies being adopted for gene therapy in sickle cell disease and early phase clinical trials appear to be promising.[2]

TRANSPLANT OUTCOME IN SICKLE CELL DISEASE

An allo-HCT should be considered standard of care when a patient has an indication and an HLA-identical sibling donor is available. The first successful cure of SCD after HSCT was reported in single pediatric patient in 1984 who had SCD and coexisting acute myeloid leukemia[3,4]. Since then, over 1,000 patients have received an HLA-identical sibling HSCT worldwide with a 5-year Event Free Survival (EFS) and Overall Survival (OS) of 91.4% and 92.9%, respectively[5,6]. EFS is lower with increasing age at transplantation and higher for transplantations performed after 2006 given improvements in preparative regimens, supportive care, and management of complications.[7] The data on transplant outcome in SCD from India is sparse, the reasons for which are numerous. Firstly, majority of patients requiring allo-HCT for their disease are either not referred to higher center in a timely manner or they do not have a matched sibling allogenic donor (found in only 10% of patients) to undergo transplant. Additionally as previously mentioned, that the hot spot areas for the severe variety of the disease requiring transplant is predominantly located in the tribal areas of Central India and Odisha where the patients are very poor to afford this treatment. However with the Government's renewed interest in the prevention and treatment of this disease at the national level, the financial roadblock for the transplant may be overcome in the near future.

INDICATIONS FOR STEM CELL TRANSPLANT IN SICKLE CELL DISEASE

It cannot be stressed enough that not all patients with sickle cell disease require an allo-HCT. In fact a majority of patients in India have a mild phenotype that with conven-

tional low cost medical intervention and occasional blood transfusions can lead a normal and productive life. An allo-HCT is always associated with a risk of morbidity and some mortality and should hence be considered with some caution. Some indications to consider an allo-HCT are listed below (adapted from Walter MC et al. NEJM 1996).[4]

- Stroke or central nervous system event lasting longer than 24 hours.
- Impaired neuropsychological function with abnormal cerebral MRI scan.
- 3 or more episodes per year of acute chest syndrome leading to recurrent hospitalizations in patients on Hydroxyurea (HU) therapy for at least 9 months.
- More than 3 episodes per year of vaso-occlusive crisis requiring hospitalizations in patients on HU therapy for at least 9 months.
- Stage I or II sickle lung disease (patients with pulmonary hypertension but without/minimal limitation of physical activity).
- Sickle nephropathy (moderate or severe proteinuria defined as urinary protein to creatinine ratio of >50 mg/mmol (442 mg/g) or a glomerular filtration rate 30 to 50% of the predicted normal value).
- Bilateral proliferative retinopathy with major visual impairment in at least one eye.
- Osteonecrosis of multiple joints.
- Red-cell allo-immunization during long-term transfusion therapy.
- Tricuspid regurgitant jet velocity (TRJV) ≥2.7 m/son2D-Echo.
- Regular RBC transfusion therapy (≥8 transfusions per year for ≥ 1 year) to prevent vaso-occlusive complications.

CONTRAINDICATIONS FOR STEM CELL TRANSPLANT IN SICKLE CELL DISEASE

- Karnofsky or Lansky functional performance score <50-70.
- Acute hepatitis with evidence of intrahepatic cholestasis or cirrhosis on biopsy.
- Severe renal impairment (GFR<30ml/min/1.73m2).
- Severe cardiac disease.
- Stage III or IV sickle lung disease (Patients with pulmonary hypertension resulting in marked limitation of physical activity).
- Demonstrated lack of compliance with medical care.

TIMING OF ALLOGENEIC HCT IN SICKLE CELL DISEASE

Young patients, preferably preschool age (2-5 years)with symptomatic SCD who have an HLA-matched sibling donor should be transplanted as early as possible. This strategy is often beneficial as it prevents permanent end-organ damage, thereby also improving the transplant outcome and quality of life. A recent risk score based on registry data would suggest that the best outcomes are seen in patients < 12 years of age with a HLA identical sibling allo-HCT.[8]

PRE-TRANSPLANT EVALUATION

A detailed pre-transplant evaluation which includes a detailed history and examination along with extensive counselling of the family is absolutely essential before proceeding with an allo-HCT. Suggested tests are listed below:

- Confirm diagnosis of patient and donor.
- Complete Blood Count (CBC), Kidney Function Test (KFT), Liver Function Test (LFT) , Urine Routine Examination.
- Coagulation Screen (PT/APTT/Fibrinogen).
- Viral Serology: Hepatitis B, C ,HIV, CMV, EBV
- S. Ferritin (Quantitative).
- Surveillance Cultures (Blood, Urine, Stool. Throat swab)
- Chest X Ray.
- HLA typing (High Resolution HLA-A,B,DQ, DR) of patient and donor.

TO ASSESS END-ORGAN DAMAGE

- CNS: Cerebral magnetic resonance imaging (MRI) and magnetic resonance angiography.
- Cerebral blood flow velocity determined by transcranial Doppler velocity
- Pulmonary : Chest X Ray; PFT (total lung capacity, forced

vital capacity, residual volume, and the ratio of forced expiratory volume to forced vital capacity), HRCT indicated only in case of strong clinical suspicion of Sickle lung disease.

- Hepatic: Liver biopsy/R2 MRI if S.Ferritin>2500ng/ml to assess hepatic iron overload.
- Ophthalmic : Fundus Examination (to r/o retinopathy)
- Renal: Urine protein/creatinine ratio, 24 hr urine protein (to r/o proteinuria).
- 2-D Echo: to r/o pulmonary hypertension.

PREPARATIVE/CONDITIONING REGIMEN

A myeloablative conditioning regimen comprising myeloablative doses of Busulfan (14-16 mg/kg in divided doses administered over 4 days); Cyclophosphamide (200 mg/kg in divided doses administered over 4 days) along with immunosuppressive doses of Rabbit ATG (10-15mg/kg given over 3 days) with either bone marrow (BM) or a peripheral blood stem cell (PBSC) as the source of hematopoietic cells has resulted in excellent OS (91-100%) & EFS (82-100%) in several studies[7,9]. The addition of ATG decreases the risk of graft rejection from 22.6% to 3% and should be considered as standard of care in HSCT myeloablative preparative regimens[9]. Methotrexate (on day +1.+3,+6,+11) along with cyclosporine (maintaining trough levels 200-300 ng/ml) is recommended as standard Graft versus Host Disease (GVHD) prophylaxis. The overall rates of acute and chronic GVHD utilizing a cyclosporine-based immunosuppressive regimen range between 10-22%, though GVHD was a main cause of treatment related mortality (TRM) in several studies.

It must be noted that there are many alterations to conditioning regimens and GVHD prophylaxis regimens that are beyond the scope of this overview, in short for haplo-identical allo-HCT and especially for T cell depleted strategies of allo-HCT with a haplo donor there are multiple options without a well-defined standard at this time. As for all allo-HCT for benign hematological disorders a bone marrow source of stem cells is preferred over PBSC. In India for all practical purposes a cord blood transplant is not performed in most centers and is hence not an option.

POST-TRANSPLANT EVALUATION

Post-transplantation, a careful follow up is required for monitoring both acute as well as chronic complications. This should be done under the close supervision by a transplant physician. A summary of the key aspects that needs to be monitored is listed below:

- Chimerism Studies – Quantitative restriction-fragment–length polymorphisms (RFLP) or tandem repeats in DNA on Day 30, 60, 90 and 365.
- Cerebral MRI with angiography: At 180 and 365 days post transplantation.
- Hypertension monitoring at each OPD visit.
- Iron Overload (S. Ferritin).
- Osteoporosis/ Avascular Necrosis.
- Pulmonary function test (Annually).
- Renal: Urine Protein/ Creatinine Ratio, 24 Hr Urine Protein (Annually).
- Ophthalmic Examination (Annually).
- To be monitored annually.
- Growth.
- 2nd Malignancy.
- Hypogonadism.
- Dyslipidemia.
- Thyroid function.

- **Vaccinations:** Inactivated or killed vaccines in all eligible patients to be initiated between 6 and 12 months after transplantation. There are various standard vaccination schedules available and it is up to the transplant physician to ensure that they administered appropriately to the post-transplant recipient, preferably after all immunosuppression has been discontinued.

WARNING SIGNS IN POST-TRANSPLANT PATIENTS

The presence of any of the following symptoms/signs in a post-transplant patient may suggest GVHD/any serious infection and warrant urgent admission or referral to higher center.

- Fever > 100.5^0 F lasting for >24 hrs.
- Loose motions.
- Redness/rash over the skin.
- Persistent vomiting.
- Dryness of mouth/eyes.
- Ulcerations in the mouth/ difficulty in swallowing.
- Significant weight loss.
- Recurrent fall in haemoglobin level.

SPECIAL ISSUES DURING HSCT IN SCD

Seizures: It is one of the most dreaded complications during/after allo-HCT particularly in SCD patients. The etiology may be multifactorial that include intracerebral haemorrhage, vasculopathy, hypoxic injury due to sickling, uncontrolled hypertension or hypomagnesemia/electrolyte disturbances. Anticonvulsant prophylaxis with phenytoin/ levetiracitam should be routinely prescribed to all the patients and continued for six months post transplantation. In addition other supportive measures like intensive monitoring of blood pressure, magnesium levels (maintained between 1.8-2.2 meq/dl), platelet count (maintained >20,000/ cumm) and haemoglobin levels (between 9-11gm/dl) should be done.

Stable Mixed Chimerism (MC): Stable mixed chimerism with a reduction rather than an elimination of haemoglobin S is sufficient to reverse the SCD phenotype as erythropoiesis by a minority of engrafted donor cells can lead to a majority of circulating normal erythrocytes with a survival advantage over short-lived sickle RBCs. In these MC regimens, donor chimerism values as low as 10% to 20% were sufficient to improve Hb levels, HbS % and SCD-related complications.[10]

Data from India: There is limited data from India especially of patients of Indian origin. A recent report presented data of 25 patients (all from sub Saharan Africa) undergoing a haplo-identical T cell replete transplant with an impressive 88% survival at 2 years.[11] Many academic centers including the authors have done a few cases which have not been systematically evaluated or reported on. Further work needs to be done to capture such data systematically.

GENE THERAPY

Gene therapy is an alternative potentially curative therapy for sickle cell disease, while early phase clinical trials are ongoing and is currently not widely available. An advantage over an allo-HCT is that the procedure uses the recipient's own stem cells and corrects the genetic defect usually with the help of an in-vitro viral vector, this is then re-infused into the patient after a conditioning regimen to provide an advantage to the infused and transduced hematopoietic stem cells over the resident stem cells in the patient. Since the stem cells are from the recipient there is no risk of Graft Versus Host Disease. Long term follow up data is still required especially for the risk of insertional mutagenesis that can cause cancer and the anticipated costs are prohibitive raising concerns about the widespread availability of this therapy for the community, more so in India.

The types of gene therapy currently being evaluated for sickle cell disease can be broadly categorized into four main groups:[2]

1. **Gene addition therapy:** this is the most widely studied and already in clinical trials. Here an additional HbS gene is added into hematopoietic stem cells in-vitro with the help usually of a lentiviral vector. The native HbS gene is not altered.
2. **Gene-editing therapy:** here usually an unrelated gene that regulates phenotype by altering for example the HbF levels is targeted. Current available therapies target the BCL11A gene, a negative regulator of HbF and by the gene editing is used to turn off the regulation of HbF in order to increase HbF production and ameliorate the phenotype.
3. **Gene silencing therapy:** Similar to gene editing the BCL11A gene, but here instead of editing the respective gene the gene product is silenced by introducing a gene to produce an antisense strand to messenger RNA of interest to silence the gene product.
4. **Gene correction therapy:** Here by various editing techniques the mutated native HbS gene is corrected.

Summary of current and upcoming clinical tri-

als is provided in the table below (from Kanter et al. Gene therapy for sickle cell disease: where we are now? Hematology Am SocHematolEduc Programme. 2021;2021(1):174-180).

RECOMMENDATION:

1. SCD patients who are manageable with standard therapy should continue with their treatment regimen.
2. Allogenic BMT may be considered in a sub-set of high risk patients with anyone of the complications/indications discussed above.
3. Myeloablative conditioning regimen with Busulfan, Cyclophosphamide and ATG are preferred.
4. Pre and post BMT management should be as per SOPs.
5. Gene therapy looks realistic, which may be available in near future.

Table 1. Current and upcoming studies of gene therapy in SCD

Study name	LentiGlobin	DREPAGLOBE	CLIMB	PRECIZN-1	Genetic silencing of *BCL11A*	MOMENTUM	CEDAR
Type of gene therapy	Gene addition	Gene addition	Gene editing	Gene editing	Gene silencing	Gene addition	Gene correction
Editing tool	NA	NA	CRISPR-Cas9 RNP	Zinc finger	ShRNA	NA	HiFi CRISPR-Cas9 RNP
Type of stem cell manipulation	Transduction	Transduction	Electroporation	Transfection with zinc finger nuclease mRNA	Transduction	Transduction	Electroporation
Vector (y/n)	BB305 LVV	DROBE 1 LVV	None	None	BCH-BB694 LVV that encodes a microRNA-adapted shRNA	γG16D LVV	Nonintegrating AAV6 donor DNA repair template
Genetic target (y/n)	NA	NA	Erythroid lineage-specific enhancer of the *BCL11A* gene	11A (*BCL11A*) locus (erythroid enhancer)	*BCL11A* mRNA	N/a	Sickle mutation (adenosine—> thymine [A—> T]
Drug product	LentiGlobin BB305	DREPAGLOBE	CTX001	BIVV003	BCH-BB694	ARU-1801[26]	GPH101
Protein product	HbA^{T87Q}	βAS3, an antisickling β-globin protein (AS3) containing 3 amino acid substitutions in the wild-type *HBB*	HbF	HbF	HbF	HbF^{G16D}	HbA

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CHAPTER 11

Immunization & Antibiotic Prophylaxis

SCD children are at high risk of serious infections with encapsulated organisms. Risk of mortality from septicemia increases by about 350 times in SCD. Risk is higher in U-5 children than other children / adults.[3] As early as six months of age, infants with SCD develop abnormal immune function because of splenic dysfunction. By five years of age most children with SCD have complete functional asplenia. Regardless of age, all patients with SCD are at increased risk of infection and death from bacterial infection, particularly encapsulated organisms such as Pneumococcus, Hib and Meningococcus.[1]

Vaccination with Pneumococcal (both conjugate & polysaccharide), Hib, meningococcal and typhoid vaccine is indicated in addition to all routine vaccines. All live vaccines may be safely given.

Currently in India, children used to get protection against Hib and Pneumococcus as a part of NIS. Those diagnosed beyond infancy should get Hib and Pneumococcal protection by catch up immunization schedule. However each should get at least one dose of PPSV23 beyond two years of age. As Typhoid and Menigococcus are not covered in NIS, they should be given in office practice.

For an Example: For a newly diagnosed four year old child with SCA who has taken all immunizations as per NIS should start one dose of PCV13, 2nd dose 8 weeks later, one dose PPSV23 8 weeks after 2nd dose of PCV13. In addition to this one dose TCV, 2 doses of MCV4 8 weeks apart to be given.

SPLENECTOMY

In patients with planned splenectomy, vaccination should be initiated at least two weeks prior to splenectomy for achieving a superior immunologic response. In those who have undergone emergency splenectomy, studies indicate that vaccination done two weeks after splenectomy is associated with a superior functional antibody response as compared to vaccination immediately following surgery.[2] Penicillin prophylaxis should be given after splenectomy.[1]

PNEUMOCOCCAL PREVENTION

Routine Vaccination

- Currently PCV is included in NIS as 2+1 schedule (6,14 weeks & nine months.)
- As per ACVIP (2020-21) 3 primary doses at 6,10,14 weeks with a booster at age 12 through 15 months.

CATCH-UP VACCINATION

- PCV & PPSV both are to be used.

NIS 2022[4]

AGE	VACCINES
Birth	BCG, OPV, Hepatitis B
6 Weeks	Pentavalent &OPV, +Rota + fIPV+ PCV
10 weeks	Pentavalent &OPV, +Rota
14 weeks	Pentavalent & OPV, +Rota + fIPV + PCV
9-12 months	MR1, JE** + PCV
16-24 months	MR2, JE**, DPTB1, OPV
5-6 years	DPTB2
10 years	Td
16 years	Td
Pregnant Mother	Td (1, 2) or Td Booster***

***** in endemic districts only***
****** one dose if previously vaccinated within 3 years***

IAP IMMUNIZATION SCHEDULE 2020-21[2]

AGE	VACCINES
Birth	BCG, OPV, HepB
6 weeks	Hexavalent1 +Rota1 + PCV1
10 weeks	Hexavalent2 + Rota2 + PCV2
14 weeks	Hexavalent3, + Rota3 + PCV3
6 months	Flu1 + TCV
7 months	Flu2, then annually till 5years
9 months	MMR1
12 months	HepA1
15 months	MMR2, Varicella1, PCVB
18 months	Pentavalent, HepA2, Varicella2
4 to 6 years	Tetravalent, MMR3
10 years	Tdap,HPV (0,6)

- For children < 6 years 2 doses of PCV13 at least 8 weeks apart.
- For children > 6 years single dose of PCV13.
- Administer PPSV23 at least 8 weeks after the last dose of PCV to children aged 2 years or older.
- An additional dose of PPSV23 may be administered after 5 years.
- PPSV23 should never be used alone.

BRANDS AVAILABLE IN INDIA:

- PCV13 (Prevenar 13 @ Pfizer).
- Prevener 13 is the most widely used PCV in the world. It is included in NIS in 102 countries. It was included in India's NIS in 2017.
- PCV10 (Synflorix @ GSK).
- Synflorix is not intended for use in adults.
- Indigenous PCV10 (Pneumosil).

After the launch of Pneumosil in december. 2020, world's most affordable PCV, Indian govt included this in NIP. As of now this vaccine is given until 2 years.

HIB PREVENTION

- As per NIS Hib is given as a component of Pentavalent vaccine at 6,10,14 weeks.
- As per ACVIP Hib is given as a component of hexavalent / pentavalent vaccine at 6,10,14 weeks & booster at 15 through 18 months.
- As of now standalone Hib is not available.

MENINGOCOCCAL PREVENTION:

- Meningococcal conjugate vaccine (MCV4, Menactra) primary dose given at 9 months along with MMR, 2nd dose given 3 months after.
- After age 2 years 2 doses of MCV4 (Menactra / Menvio) given 8-12 weeks apart. A booster dose should be administered every 5 years. [3]

TYPHOID PREVENTION:

- A single dose of TCV is recommended from the age of 6 months onward routinely.
- For a child who has received only typhoid PS vaccine, a single dose of TCV is recommended.
- Routine booster of TCV is not recommended as of now.

BRANDS AVAILABLE IN INDIA:

- Typbar TCV @ BBIL.
- Zyvac TCV @ Zydus Cadila.
- TyphiBev @ BE.
- Enteroshield @ Abbott, 0.5ml PFS.

FLU PREVENTION

- Yearly Flu shots are given.[1]
- If flu is given for first time beyond 6 months till 8 years , 2 doses to be given 1 month apart. There after annual shots are given.
- Though AAP recommend annual flu shots India being in hot climatic zone ACVIP endorse flu shots till 5 years of age like the schedule for normal children.

BRANDS AVAILABLE IN INDIA:

- Fluarix tetra @ GSK.
- Influvac tetra @ Abbott.
- Fluquadri @ Sanofi.
- Vaxiflu-4 @ Zydus.

RECOMMENDATION:
In addition to Routine Immunizations specific immunizations like Pneumococcal, Hib, Menigococcal and Typhoid are highly recommended.

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PENICILLIN PROPHYLAXIS

Children with SCD are at substancially increased risk for invasive pneumococcal disease; daily antibiotic prophylaxis untill the age of 5 significanty reduces the risk. Daily penicillin prophylaxis decreases episodes of pneumococcal bacteremia.

Splenic dysfunction begins as early as 3 months in infants with HbSS. All these children should be started on prophylactic Penicillin as early as 2-3 months of age.This prophylaxis should continue for a minimum of 5 years. No established guidelines exist for Penicillin prophylaxis beyond 5 years of age.[2]

Continue prophylactic penicillin beyond 5 years if child has undergone a splenectomy or had an pneumococcal invasive disease.

1. Oral Penicillin V potassium.

62.5mg/bd < 1 year.
125mg/bd after 1y till age of 5 years.
250mg/bd after 5 years.

Amoxycillin is not a good choice as it has not been studied to see effectiveness at preventing infection in SCD. It causes more side effects and puts patients at increased risk for development of resistant organisms.

2. Patients allergic to Penicillin macrolides like Erythromycin / Azithromycin can be used.

Erythromycin 125mg/bd less than 5 years age Azithromycin 6mg/kg/d.

CONCLUSION

In India Penicillin V is not available. The brand which is available in India is Pentid , a Penicillin G Potassium. This form of Penicillin is typically used in IV or long acting injectable formulation due to poor oral absorption. This is the reason where option for antibiotic prophylaxis remains with Erythromycine/ Azithromycine.

However all data regarding effectiveness of Penicillin prophylaxis belong to US & other develped world, a country like India where we deal with mostly Asian haplotype SCD where most patients present with pneumococcal disease at a later age in contrast to African haplotype presenting as earlier age.

RECOMMENDATION:
Pneumococcal vaccination is mandatory in comparision to Penicillin prophylaxis in SCD children (U-5) in our country.

CHAPTER 12

Monitoring

Sickle cell diseases (SCD) are a group of inherited,autosomal recessive hematological disorders caused due to point mutation (G6V) in the β-globin chain of haemoglobin (Hb) resulting in formation of HbS, which is an abnormal haemoglobin.[1] This can damage any part of the body starting right from the brain till the legs and can affect every organ and organ systems. Hence, regular monitoring is advised for early-stage detection of SCD and its complications in order to avoid the end-organ damage which can lead to improved quality of life in these patients.

As the sickle cell disease is more prevalent in tribal areas in various states across the country, a uniform guideline should be practiced in managing as well as monitoring the patients.[2]

MONITORING OF CEREBROVASCULAR DISEASE

The reported incidence of pediatric stroke is generally 300 times higher in SCD patients than the general population. Overt stroke occurs in up to 11% of children with SCD by age 18-24 and around 24% by the age 45. The risk of stroke is highest during the first decade, and it is most significant between ages 2 and 5, when it reaches 1.02% per year.[3] The prevalence of stroke in Asian patients with sickle cell anaemia was reported to be 5% (95% CI: 4%, 6%) with a range of 1–41%, in a pooled metadata analysis.

In this monitoring approach, Transcranial Doppler (TCD) measurements of blood flow velocities in the major cerebral arteries are predictors of stroke risk in HbSS/HbSB0 at ages 2 to 16 (4). In children (with SCD) the rate of silent cerebral infarcts is up to 39% whereas in adults, it is reported to be 43% and thus, these patients are associated with neurocognitive deficits and increased risk for overt strokes.[5]

THE FOLLOWING FACTORS INCREASE THE RISK OF STROKE IN SCD PATIENTS:

(i) Elevated cerebral blood flow velocity by transcranial Doppler.
(ii) Obstructive sleep apnea and nocturnal hypoxemia.
(iii) Silent cerebral infarctions.
(iv) Hypertension.
(v) Atrial fibrillation & Patent Foramen Ovale.

The screening parameters for silent cerebral infarcts include:

(i) Baseline cerebral MRI/magnetic resonance angiography at age 10 years (without sedation).
(ii) Neurocognitive testing for any child with difficulties in school, abnormal transcranial Doppler, or MRI.
(iii) Evaluation by a neurologist.

MONITORING OF CARDIOVASCULAR DISEASE

Ischemic heart disease, left ventricular dysfunction, and congestive heart failure are associated with mortality in adults with SCD. Pulmonary hypertension occurs in more than 30% of adults with SCD and is associated with an increased risk of mortality. Ischemic heart disease, left ventricular dysfunction, and congestive heart failure are associated with mortality in adults with SCD. Pulmonary hypertension is the average of pulmonary artery pressure estimated by tricuspid regurgitant having a jet velocity of 2.5 m/s or greater on Doppler echocardiogram. It is associated with diastolic dysfunction, but both are independent predictors of mortality in adults and are seen less frequently in children.[6,7]

The screening guideline, parameters include:

(i) Screening transthoracic echocardiogram at the age 10 (with an interval of every 2 to 5 years).
(ii) Evaluation of obstructive sleep apnea, hepatic dysfunction, and chronic kidney disease.
(iii) Evaluation of right ventricular function with tricuspid annular plane systolic excursion.
(iv) Evaluation of tricuspid regurgitant jet velocity, diastolic dysfunction (mitral valve E/A velocity and lateral left ventricular E/e' ratios) and left ventricular function.

(v) If repeated evaluation of tricuspid regurgitant jet velocity is 3.0 m/s or greater at clinical baseline, then obtain a 6-minute walk test, pulmonary function tests, and NT-pro BNP. It also should exclude obstructive sleep apnea, hepatic abnormalities and chronic kidney disease.

(vi) Cardiological intervention for Right heart catheterization, when indicated.

MONITORING OF PULMONARY COMPLICATIONS

In SCD patients, the pulmonary complications include acute chest syndrome, chronic sickle lung disease airway hyperreactivity, pulmonary hypertension, and sleep disordered breathing. Monitoring of additional complications can aid to disease understanding and diagnosis.

The screening guideline, parameters include:

(i) Familial history of allergy, asthma, or atopic dermatitis.

(ii) Identification of history of wheezing, shortness of breath, night-time cough, and frequent upper respiratory infections.

(iii) Identification of allergies, chronic rhinosinusitis, obstructive sleep apnea, and gastroesophageal reflux.

(iv) Test for monitoring of acute chest syndrome, pulmonary function tests at age 8 or older, peak expiratory flow rate. Repeated periodic screening to monitor for restrictive changes.

MONITORING OF RENAL COMPLICATIONS

In SCD patients, the renal complications involve sickle cell nephropathy (SCN) which is characterized by altered haemodynamics in renal circulation, proteinuria, chronic kidney disease, acute kidney injury, impaired urinary concentrating ability/ hyposthenuria, distal nephron dysfunction, haematuria, and increased risks of urinary tract infections.[8]

The screening guideline, parameters include:

Enquire for NSAID abuse and exclude analgesic induced nephropathy.

(i) Monitoring of blood pressure and haemoglobin at all visits.

(ii) Annual urine analysis (urine albumin/creatinine ratio) from 10 years of age and if abnormal, analyze the first morning void urine. If microalbuminuria or macroalbuminuria is observed, then 24-hour urine protein analysis is to be done.

(iii) Monitor potassium level and estimate the glomerular filtration rate and stage of chronic kidney disease.

(iv) Consult a nephrologist for hypertension, proteinuria, a creatinine of greater than 0.7 mg/dL in children and greater than 1.0 mg/dL in adults.

(v) For gross or microscopic hematuria, a renal ultrasound examination is done to diagnose papillary necrosis and rarely, renal medullary carcinoma.

MONITORING OF HYDROXYUREA IN SCD PATIENTS AFTER TREATMENT

Hydroxyurea, is the only widely available, affordable and effective drug to reduce the frequency of painful episodes in SCD patients. It is able to ameliorate the VOCs by various mechanisms discussed elsewhere. Being a cytotoxic drug, its monitoring is essential so as to achieve maximum benefit with minimal side effects.[9]

The screening guideline parameters include:

(i) Baseline complete blood count/ differential (absolute neutrophil count), reticulocyte count, creatinine, and liver function tests (ALT, bilirubin) – before starting hydroxyurea.

(ii) High-performance liquid chromatography at baseline and thereafter to monitor adherence of drug intake.

(iii) Monthly complete blood count for monitoring myelosuppression.

(iv) Efficacy of the drug can be assessed by reviewing history (crisis, admissions, and blood transfusions), mean corpuscular volume, white blood cell count, reticulocyte count, bilirubin and lactate dehydrogenase.

MONITORING OF CHRONIC BLOOD TRANSFUSION & ITS COMPLICATION

Blood transfusion is not required for all sickle cell disease patients. But, those on chronic transfusion therapy for complications of SCD need to be monitored.[10] Transfusion increases the total Hb level while proportionately decreasing

the HbS level in the circulation. Thus, it increases the oxygen carrying capacity while decreasing the adhesiveness of the blood corpuscles. Monitoring of serum ferritin (SF) is essential to identify and start iron chelation in patients with iron overload. However, relationship of SF with total body iron is not linear after 20 units of blood transfusion or SF value of 1500-2000 or higher. [11] Reverse also occurs while monitoring of chelation therapy; lowering of iron load is not reflected by SF even at 1 year. [12] Hence, cardiac MRI T2*, Liver R2*, liver iron concentration (LIC), are alternative tools to determine the exact iron overload.

The screening guideline, parameters include:

(i) Transfusion should be avoided at haemoglobin levels of greater than 10 g/dL to avoid hyperviscosity.

(ii) Red blood cell phenotyping should be done before the start of transfusion, and screening for allo-antibodies to be carried out to prevent allo-immunization.

(iii) Extended phenotypically matched blood (D, Cc, Ee, Kell, Kidd, and Duffy) should be transfused to have an optimal Hb increment.

(iv) Complete blood count, reticulocyte count, type and screen before first and then each subsequent transfusion.

(v) Annual screening of hepatitis/human immunodeficiency virus for monitoring transfusion transmitted infections.

(vi) Monitoring for iron overload and chelation toxicity includes –3-6 monthly serum ferritin, renal and hepatic function, annual audiology and ophthalmology screenings. Measurement of hepatic iron overload by MRI liver R2* and cardiac iron deposition by cardiac MRI T2* is recommended.

OTHER SYSTEMIC MONITORING INCLUDES

(1) Ophthalmology evaluation for retinopathy at age 10 and biannually if normal.

(2) Bone density evaluation at age 10, and reevaluation if abnormal.

(3) Radiologic assessment of hip joints, knees and lumbo-sacral spine or other bones for avascular necrosis and osteomyelitis of bones, if symptomatic.

(4) Vitamin D level monitoring and supplementation if <30 IU.

(5) Screening for dyslipidemia, T2 diabetes mellitus and hypertension in older adults with SCD to initiate after 40 years.

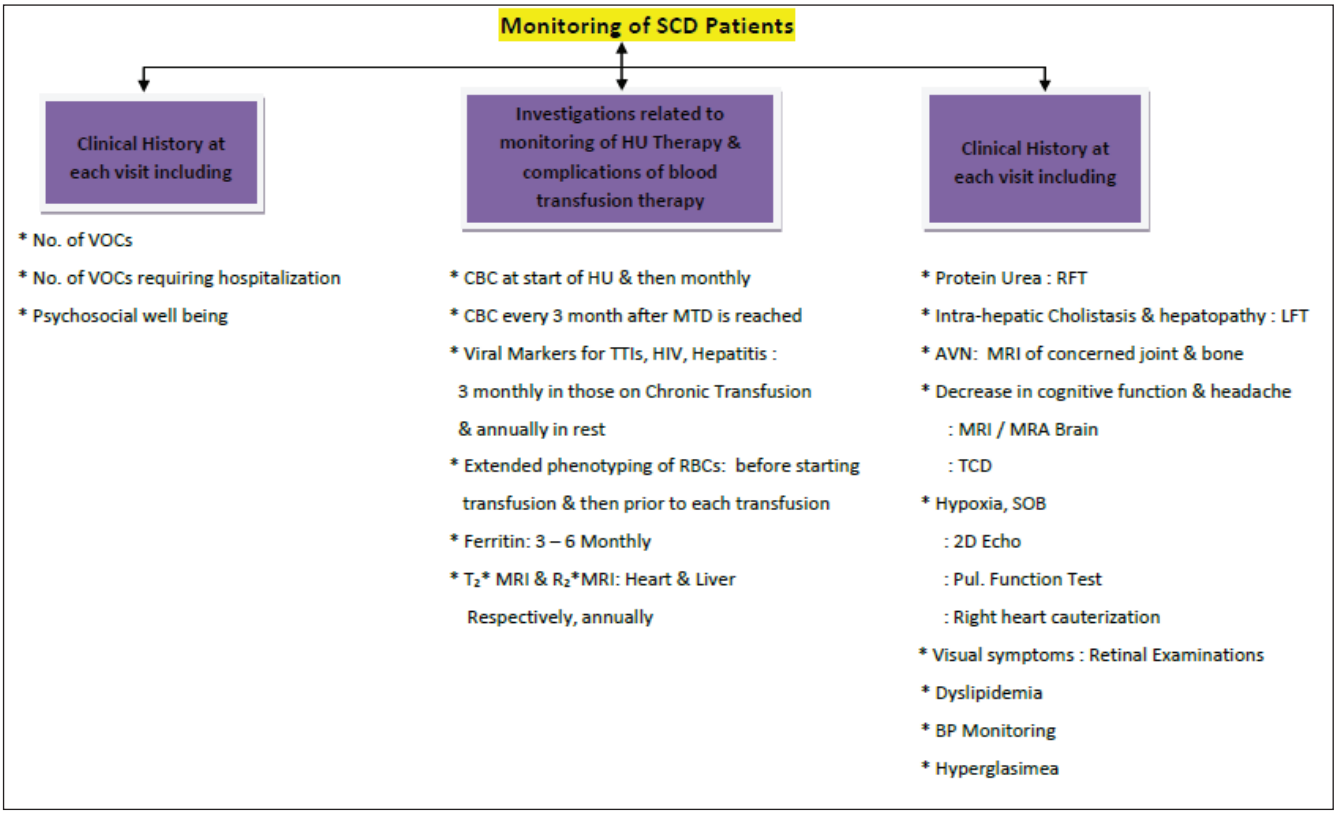
RECOMMENDATION:

INVESTIGATIONS	FREQUENCY	COMMENTS
CBC with reticulocyte count	3 monthly	To see response of HU Monitor ANC and platelet count for HU side effects
Extended phenotyping of RBCs	Before 1st Transfusion of PRBC	To minimize chance of alloimmunization
Renal function test	3 monthly	Adverse effects of HU Renal complications of SCD
Liver function test	3 monthly	Adverse effects of HU
Transcranial Doppler	Annually after 2 years of age till 16 yrs	For stroke prevention and screening
Screening MRI	At least once at 10 yrs age	To evaluate cerebrovascular infarct or silent brain infarcts
BP and oxygen saturation Measurements	Every visit	Screening for cerebrovascular disease (CVD), obstructive sleep apnea (OSA), pulmonary hypertension, and chronic pulmonary disease
Overnight oxygen saturation measurement	Low oxygen saturation in OPD visit	Screening for CVD and OSA
Pulmonary function tests	Low oxygen saturation (<95%)	Rule out chronic sickle pulmonary complications
Bone Density	At 10 years age	Nutrition consultation and re-evaluation if abnormal

RECOMMENDATION:

INVESTIGATIONS	FREQUENCY	COMMENTS
2D echocardiography	At least at 10 years age & every 2-5 years, if normal	Screening for pulmonary hypertension & diastolic dysfunction
6 min walk test & NT Pro BNP	Annually	Only if features of pulmonary hypertension are present
Urine analysis and specific gravity, urine albumin by creatinine ratio ACR	Annually after 3–5 years of age	To screen renal complications of SCD
HIV/HBsAg/HCV	Annually	Children requiring intermittent or regular transfusions
T2*MRI heart and R2* MRI liver	Annually	Evaluation of iron overload status
Ferritin	3–6 monthly	Evaluation of iron overload status
Retina screening	Biannually after 10 years of age	To detect early proliferative sickle retinopathy
MRI scans	Persistent painful hips or shoulders	To rule out avascular necrosis
Psychological, educational, and social interventions	Annually or when required	Improve quality of life. Assess cognitive abilities and behavioral issues

FIGURE: 1



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CHAPTER 13

Management Of Pregnancy

1. PURPOSE AND SCOPE

The objective of this ICH guideline is to propose the management of pregnant women with SCD (HbSS, HbS/β^0 Thalassaemia, HbS/β^+ Thalassaemia, HbSC etc) in India. It includes pre-conceptual counselling / screening, antenatal intra-partum and postnatal management.

2. BACKGROUND & INTRODUCTION

SCD is one of the most commonly inherited conditions worldwide. There are five different Haplo types: Senegal, Benin, Central African Republic (CAR or Bantu), Cameroon and Arab-Indian (or Asian). The severity of the phenotype varies widely and the Arab-Indian Haplo type has the least severe clinical course which is predominantly due to presence of raised of HbF that inhibits HbS polymerization.

SCD patients in India belong to Arab-Indian Haplo type mostly. They are leading a symptom-free prolonged life with regular administration of Hydroxyurea (HU) and other supportive and preventive measures. As a result most of these patients are getting married and expressing their desire to have children.

Pregnancy with SCD Anaemia is of high risk category with increased maternal complications such as anaemia, vaso-occlusive (VOC) crises, acute chest syndrome (ACS), jaundice, maternal mortality, preeclampsia, urinary tract infections, etc.

The Indian studies have reported various complications: low birth weight (16.5% to 100%), prematurity (16.6% to 72%), IUGR (3.3% to 50%), still birth (3.7% to 25.5%) and neonatal death (0% to 8.3%) etc. [1 to 11] There is paucity of evidences to recommend the management of SCD in pregnancy and vice versa due to lack of adequate randomized controlled trials. However, the following recommendations are based on available data, extrapolation of the evidences and consensus expert opinion.

1. PRECONCEPTION CARE

A thorough discussion regarding the pros and cons of conception and pregnancy should be done with women, partner and family members (whenever needed). This should include the reproductive options (Surrogate Pregnancy, Adaptation) partners screening, optimization of management at different stages and review of teratogenic medication, etc.

RECOMMENDATION:

1. ***The women with SCD and her husband should accept pregnancy at their own risk as there are no reliable predictors of the risk, morbidity and mortality related to pregnancy.***

3.1 GENETIC SCREENING

Woman with SCD whose partner is a carrier of other Hb Pathy gene will have a risk of up to 50% in each pregnancy of having a child with a sickling disorder.

RECOMMENDATION:

1. ***All women with SCD should undergo with partner testing prior to the initiation of pregnancy.***
2. ***High risk couples (Both carrying the Hb Pathies genes) should be counselled for reproductive options, prenatal diagnosis or pre-implantation genetic diagnosis (PGD).***

3.2 PRE-CONCEPTION COMPREHENSIVE REVIEW OF COMPLICATIONS

Prior to pregnancy the women should have comprehensive evaluation of general health, cardio-vascular system including eco-cardiography, renal function, urinary protein (albumin / protein: creatinine ratio, pulmonary function test, neurological evaluation and various complications of SCD. [12 - 13] The management should be optimized before em-

barking on pregnancy.

RECOMMENDATION:

1. ***Conception and pregnancy should be discussed in Annual Medical Review.***
2. ***All women should be examined and managed by necessary special investigations as per the need prior to the pregnancy.***

3.3. PRE-CONCEPTION MEDICATION REVIEW

A detailed review of the medications should be done prior to the conception. Folic acid is recommended daily before, during and after pregnancy.[13 - 14] Vitamin D deficiency is common across the India. It should be prescribed as a supplementation during pregnancy.[15]

Patients with SCD are prone for infection due to non-functioning of spleen. Penicillin prophylaxis may be considered in those patients with features of recurrent infections. Paracetamol and codeine containing analgesic are safe and effective and considered as first line therapy for pain management.[16-17] If not effective, NSAIDs can be used with caution before 12 weeks and avoided after 13 weeks as it increases the risk of premature patent of the doctors.[16]

Opioid use can be assessed by a special chronic painting. Potential terratogenic medications like angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptors (ARBs), HU, iron chelators, etc should be reviewed and necessary replacement or stoppage should be done depending on the case. HU is teratogenic in animals, should be stopped 3 months prior to the plan conception and is not recommended in any time of the pregnancy. There are reports in the literature where women have received HU in pregnancy both for SCD and for other indications and some of them have continued it throughout pregnancy without adverse effect on the baby.[1, 18 – 21]

The management of complications of SCD during pregnancy is challenging. As a substitute to HU, regular red cell erythrocytapheresis, or simple exchange transfusion (upper limit of Hb is 10 gm%). This alternative may not be suitable to those women who are not able to receive blood transfusion because of multiple red cell allo-antibodies or previous severe delayed haemolytic transfusion reactions. For these women, we suggest a discussion between haematologists, obstetricians and women prior to pregnancy regarding information related to risk and benefits of continuing HU therapy throughout pregnancy to aid patient-led decision making. These women should undergo frequent fetal monitoring to detect any abnormalities at earliest.

Iron chelators are not recommended during pregnancy as these are still regarded as potential teratogenic. These drugs should be stopped before conception. If there is evidence of Iron overload, this should be treated prior to the conception. P Mohanty etal (2017) noted disproportionate anaemia in 9.6% of cases of SCD (HbSS) due to iron deficiency in Eastern India while equal percentage of cases did reveal iron overload (Sr. Ferritin > 1000 ng/mL) requiring iron chelation.[22]

These patients with evidence of iron deficiency can be administered iron therapy to improve the Hb level. The incidence of Methylcobolamine deficiency is more than 50% of Indian population due to the peculiar Indian diet. There is consensus to administer Methylcobolamine Injectable or other preparation in usual dosage to all the patients unless there is any contraindications.

New medications including Crizanlizumab, Voxelotor and Glutamine are not approved to use during pregnancy and should be stopped prior to conception.

RECOMMENDATION:

1. ***Folic acid: 5 mg daily to all women before conception and throughout pregnancy.***
2. ***Vitamin D & Calcium Supplementation: May be considered if there is no contra indication.***
3. ***Antibiotic prophylaxis: If there is features of recurring infections.***
4. ***Vaccination: Seasonal or others as per the need.***
5. ***Terratogenic drugs like ARBs, ACEi should be replaced with safer drugs***
6. ***Hydroxychloroquine: Should be discontinued 3 months prior to conception.***
7. ***Alternative therapy with Red Cell transfusion or***

continuation of HU after 1st trimester should be discussed and instituted as per the need on case basis.

8. ***Iron chelators: Should be stopped before conception and throughout the pregnancy. Iron overload should be treated preferably before conception.***
9. ***Iron Supplementation: Those women having evidence of iron deficiency (Disproportionate anaemia and low serum ferritin / transferrin saturation) should be supplemented with Iron therapy till normalization preferably before pregnancy. These women should receive Iron supplementation throughout the pregnancy like that of others.***
10. ***Methycobolamine: Injectable Methylcobolamine or other legitimate preparation should be given in the usual dosage before and throughout pregnancy.***

1. ANTENATAL CARE

1.1 ANTINATAL HbPATHY SCREENING

The objective is that any woman of SCD who has a potentially affected child with HbPathy or whose partner is a carrier of HbPathy should receive appropriate counselling, evaluation of partner and prenatal diagnosis by chorionic villus sampling (around 12 weeks or amniocentesis). If the fetus is diagnosed to suffer from major Hb-pathy disease, the termination of the pregnancy should be taken up. Studies are on-going using non-invasive prenatal diagnosis via detection of cell free fetal DNA in the maternal circulation, but this approach is not available in India.[23]

RECOMMENDATION:

1. ***Before pregnancy the partner of the woman should be offered partner testing.***
2. ***PND @ 12 weeks followed by continuation or termination of the pregnancy if the fetus is likely to be healthy or diseased respectively.***

1.2 MATERNAL HEALTH

This includes the review of vaccinations, review of medications, assessment for organ damage, red cell allo-antibodies, iron status and methycobolamine deficiency at an early stage. The mainstay of antenatal care is evaluation, prevention and management of routine general care during pregnancy and SCD specific complications as per SOPs respectively. Both clinical and laboratory investigations should be done once in a month but depends on medical progress and the presence of medical complications.[24] Obstetricians, Haematologists and other related specialists as per the need should evaluate and help in the management after regular joint discussion.

1.3 PREGNANCY–INDUCED HYPERTENSION

Women with SCD have an increased risk of pregnancy-induced hypertension and preeclampsia.[25 – 27] Low dose aspirin prophylaxis is recommended at 75 – 250 mg daily from 12 weeks of gestation for high risk of preeclampsia [27 – 28] unless there is any contraindication. Aspirin should be stopped at 36 weeks to prevent any chance of increase post-partum haemorrhage. [29] Close monitoring for preeclampsia should be done and the target blood pressure of < 130 /80 mm Hg should be maintain. [12]

RECOMMENDATION:

1. ***A full assessment including review of vaccination, medications, organ damage and red cell allo-antibodies should be done before and during pregnancy.***
2. ***Antenatal care should be provided by a multidisciplinary team including an obstetrician, haematologists and other specialists.***
3. ***Folic acid: 5 mg daily***
4. ***Vitamin B and Calcium supplementation***
5. ***Iron Supplementation: Should be given if there is laboratory evidence of iron deficiency***
6. ***Methylcobolamine: Injectable or other preparation in usual dosage.***
7. ***Low dose aspirin: 75 – 150 mg per day from***

12 weeks of gestation. Should be reviewed at 36 weeks of gestation to considered stopping.

1.4 SCHEDULED ULTRASOUND SCANNING

Women should be offered serial fetal biometry scans (growth scans) every four weeks from 24 weeks gestation.[30]

1.5 BLOOD TRANSFUSION IN PREGNANCY

Transfusion can be helpful to correct severe anaemia, reduced pregnancy complications and sickle-related complications. However, blood should be CMV negative, HbS negative and matched for extended phenotype including full rhesus typing (C, D & E) as well as Kell typing to reduce the incidence of allo-antibodies < 5% and delayed haemolytic transfusion reaction.[31] Thus the benefit of transfusion vis-à-vis with the risk of transfusion should be discussed and implemented very carefully. There is no reliable evidence-based parameter to recommend transfusion-based or alternative therapy as per the need during pregnancy. Similarly there is little evidence to recommend any target Hb or Hb% during pregnancy.

Simple transfusion on demand may be tried if the prophylactic transfusion is thought to carry significant risk. There is no evidence to recommend any optimal Hb level or Hbs % prior to C-Section.[31-32]

RECOMMENDATION:

1. ***If needed transfusion should be given; ABO-compatible, extended Rh- and Kell matched, CMV Negative and HbS Negative. If there is any presence of red cell antibodies in the patient then the donor red cell should be negative for the corresponding antigen.***
2. ***Prophylactic Transfusion: The risk and benefits should be discussed.***
3. ***Not routinely recommended. It Should be considered on case basis.***
4. ***Long Term Transfusion.***

a. ***Should be considered for women who are receiving prior or stroke prevention.***

b. ***Women with worsening anaemia or acute SCD complications (ACS / Stroke) in pregnancy.***

1.6 MANAGEMENT OF ACUTE PAIN EPISODES DURING PREGNANCY

Pregnancy is associated with an increased incidence of VOC due to increase in physical / psychological stress, dehydration, worsening anaemia, pro-coagulant stroke and increased risk of infection. All pregnant women should have a prior pain management plan with multidisciplinary team. There are no randomized control trials among pregnant woman with SCD presenting with VOC. Thus the VOC should be based on the principle of non-pregnant SCD patients.

Thromboprophylaxis with LMWH should be administered for women with SCD presenting with VOC unless there is a contra-indicatory.[33] Frequent monitoring of the fetus as well as of the mother is essential in this medical emergency.

RECOMMENDATION:

1. ***Prospective VOC management by Multidisciplinary team should be for all women.***
2. ***The principle of management: Same as non-pregnant counterparts.***
3. ***NSAIDs: Should be used with caution in 1st trimester and avoided after 31st weeks of gestation.***
4. ***LMWH: Should be given to all women at usual dosage presenting with VOC or during any antenatal hospitalization.***

1.7 MANAGEMENT OF ACUTE CHEST SYNDROME & OTHER COMPLICATIONS:

As per the principles and SOPs of non-pregnant counterparts there is no evidence-based recommendation specific to pregnancy.

1.8 MANAGEMENT OF VTE AND THROMBOPROPHYLAXIS

Both pregnancy as well as SCD are hyper-coaguable conditions. Thus all women with SCD should undergo risk assessment evaluation and should be considered for prophylactic LMWH from 20 weeks of pregnancy until 6 week of post-partum.

In the presence of any additional risk factor, prophylaxis should start in the beginning of pregnancy. Woman admitted for VOC should be offered LMWH throughout the hospital stay unless there is contraindicatory.

RECOMMENDATION:

1. ***All women with SCD should have risk assessment at an early date.***
2. ***LMWH at usual dosage:***
3. ***From 28 weeks of pregnancy till 6 weeks of post-partum.***
4. ***Start from the beginning of pregnancy if there are any additional risk factors.***
5. ***LMWH at usual dosage: Hospitalization for VOC throughout the admission unless there is contra indication.***

2. INTRA-PARTUM CARE

2.1 TIMING OF BIRTH

There are no RCTs to recommend the appropriate timing of delivery. Due to the increase risk of placental insufficiencies and preeclampsia delivery between 38 and 40 weeks is preferable to prevent complications adverse perinatal outcomes at late pregnancy.

RECOMMENDATION:

1. ***Normal growing baby should be deliver between 38 – 40 weeks of gestation***

2.2 MODE OF BIRTH:

The mode of delivery should be decided based on obstetric indications.[17, 25-26]

2.3 OPTIMAL INTRA-PARTUM CARE

The principle of optimum intra-partum care includes best analgesia In consultation with anaesthetics, avoidance of stress, infection, dehydration, avoidance of protracted labour and regular monitoring of oxygen saturation. General anaesthesia and pethidine should be avoided. The delivery should be preferably done in a tertiary health care system with availability of all facilities like Hematology facilities, blood transfusion facilities, ICU facilities, etc. Epidural anaesthesia is safe and effective and should be available for women in labour room.[34]

RECOMMENDATION:

1. ***It should be considered as high risk pregnancy and managed in tertiary care centre with all facilities including services of Hematology, paediatrics, blood bank and ICU, etc.***
2. ***Blood components after extended cross matching (Rh- Kell), CMV Negative, HbS Negative should be administered if needed.***
3. ***Continuous monitoring of the mother and fetus and management as per the need.***
4. ***Opiates / NSAIDs may be used for analgesia except for pethedine.***
5. ***Regional analgesia is recommended for C-section.***

3. POSTPARTUM CARE

3.1 OPTIMAL POST-DELIVERY CARE

These women are prone for thrombosis and VOC during this period. VOC should be managed as per the SOPs. LMWH should be continued 6 weeks post-delivery. [35] Breastfeeding should be encouraged; HU and other routine management of SCD should be started early.

3.2 CONTRACEPTION ADVICE FOR WOMEN WITH SCD

Medications which enhance the risk of thrombosis should be avoided. Progesterone only preparation like progester-

one pill, injectible contraceptives and the Levonorgestrel intrauterine system (LNG-IUS) are preferable. The benefit of copper intrauterine device outweighs the risks. The barrier methods are safe with SCD but generally less effective.

CONCLUSION

Many women with SCD in India are now in a position expressing strong desire to have pregnancy. The pregnancy in women with SCD is of high risk category with increase complications of fetus, mother and SCD specific complications. The management includes the optimal treatment of SCD, fetus as well as mother. Every mother with SCD should offer the benefit of evaluation of partner and PND at early stage. The optimal outcome depends on professional management of by a multidisciplinary team and should be taken up in a tertiary health care system with all facilities. There are no RCT-based evidences to recommend the management of all stakeholders in this scenario. The opinion expressed is based on limited studies, extrapolating the data and by consensus opinion of experts. RCT-based recommendation for different aspects of management of women with SCD in pregnancy is unmet medical need which should be taken up by medical paternity on a priority basis in future.

TABLE 1. MATERNAL AND FETAL COMPLICATIONS IN WOMEN WITH SCD

COMPLICATIONS

Maternal complications of pregnancy

Increased maternal mortality.
Hypertension syndromes—preeclampsia and eclampsia.
Venous thromboembolism.
Increased pain (acute, chronic, or recurrent acute) and other SCD-related complications, including infection, acute chest syndrome, acute exacerbation of anaemia, and acute splenic sequestration.
Worsening steady-state anaemia.
Proteinuria, worsening of renal disease.
Hepatic dysfunction, worsening of hepatic disease.

Fetal complications of pregnancy

Mortality.
Prematurity.
Growth problems—intrauterine growth restriction and small for gestational age.

TABLE 2. MANAGEMENT RECOMMENDATIONS FOR PREGNANT WOMEN WITH SCD

TRIMESTER

First trimester/initial visit

General recommendations :
Identify and establish a communication plan with members of multidisciplinary team, including a specialist in SCD and high-risk obstetrical care.
Establish frequency of routine visits throughout pregnancy.
Test for and treat iron defificiency.
Start folic acid supplementation—5 mg daily.
Discuss need for penicillin prophylaxis, particularly in women with a past history of pneumococcal sepsis.
Vaccinate for encapsulated organisms and hepatitis B if not administered previously; administer influenza vaccine.
Discuss low-dose aspirin therapy—consider starting aspirin 75-81 mg daily at 12 wk gestation; for patients with prior preeclampsia, renal disease, or hypertension, discuss higher doses of daily aspirin.
Discuss VTE prophylaxis—compression stocking use daily and low molecular weight heparin prophylaxis during hospitalizations; for patients with permanent venous catheters, discuss daily low molecular weight heparin.
Close monitoring for hypertension—establish baseline blood pressure and monitor blood pressure frequently
Regular monitoring of fetal growth by ultrasound.

Routine screening for bacteriuria.
Establish steady-state values.
Pulse oximetry.
Blood pressure.
Haemoglobin phenotype/genotype.
Haemoglobin and reticulocyte count ranges.
Red cell antigen phenotype or genotype.
Red cell antibodies—both present and transient.
End-organ damage assessment.
Echocardiogram.
Urine protein assessment.
Pulmonary function tests.
Ophthalmologic examination.
Evaluation for iron overload.
Screen for red cell alloimmunization.

Medication evaluation
Discontinue hydroxyurea, warfarin, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers; chelation therapies; and consider substitute therapies; chelation therapies.
Genetic counselling and patient education
Haemoglobin electrophoresis on patient's partner/father of child.
In-person meeting to discuss test results and educate on potential outcomes of pregnancy for mother and child, including both positive and negative events.
Develop plans for pain management, end-organ damage and blood pressure monitoring, red cell transfusions, and fetal monitoring.
Pain management
Analgesics to be used according to trimesters.
Identification of hospital team to manage pain and hospital unit location.
Monitoring of fetus during inpatient stays
Use of anticoagulation for VTE prophylaxis.
End-organ damage and blood pressure monitoring
Urinalysis, glomerular filtration rate, and proteinuria assessments monthly.
Establish, document, and communicate systolic and diastolic steady-state ranges for patient before pregnancy.

Blood pressure monitoring during pregnancy every 2-4 wk with high-risk pregnancy care are key members of the health care team.2 Other specialists to consider include a neonatologist, an anesthesiologist, a transfusion medicine specialist, and a pain management expert. An individualized plan to monitor SCD-related complications, need for transfusion therapy, the fetus for growth abnormalities, and blood pressure for development of preeclampsia is strongly recommended. (Table 2).

TABLE 2. (CONTINUED)

TRIMESTER

Red cell transfusions.
Establish haemoglobin goals at steady state and during inpatient admissions.
Monitor complete blood count and reticulocyte count every 2-3 months.
Establish indications for intermittent red cell transfusions.
Establish indications for chronic/prophylactic transfusions.
Communicate appropriate red cell antigen matching—at minimum.
ABO, D, C, E, Kell; consider further extended antigen matching based on red cell alloimmunization and history of delayed hemolytic transfusion reactions.
Establish post-transfusion haemoglobin and haemoglobin S percentage goals.
Fetal monitoring.
Fetal ultrasound at 7-9 wk; recommend every 4 wk through 24 wk and then, every 2 wk to monitor fetal growth.
Biophysical profile during inpatient stays.

SECOND TRIMESTER

Revise first trimester management plans if necessary
Develop a plan for delivery, including plan for Cesarean Section
Educate mother and her support system about compli-

cations that may occur during and after delivery as well as possible need for neonatal intensive care unit stay for infant.
Communicate plans to members of multidisciplinary team.
Revise frequency of routine visits.
Test for and treat iron deficiency.

THIRD TRIMESTER

Include neonatologist in discussions about fetal growth, plans for delivery, mother's alloimmunization status, and use of opioids throughout pregnancy.
Revise first/second trimester management plan if necessary.
Revise plan for delivery, including plan for Cesarean Section and whether transfusion before delivery is required.
Discuss pain management postpartum and need for initiating/restarting pre-pregnancy disease-modifying therapies; plans may need modifification according to whether the patient plans to breastfeed.
Develop plan for VTE prophylaxis post delivery.
Develop plan for screening infant for neonatal abstinence and hemolytic disease of the newborn.
Communicate plans to members of multidisciplinary team.
Revise frequency of routine visits.
Test for and treat iron deficiency.

TABLE 3. SCREENING FOR CHRONIC DISEASE COMPLICATIONS

SCREENING

Pulmonary hypertension and prolonged QTc—echocardiogram, electrocardiogram.
Proteinuria and high blood pressure—urinalysis, renal function tests, urine creatinine/protein, serum creatinine, assess glomerular filtration rate,
consider renal ultrasound.
Hepatopathy/gallbladder disease—liver size, aspartate aminotransferase, alanine aminotransferase, bilirubin levels, abdominal ultrasound.
Splenomegaly/hypersplenism—physical examination and splenic ultrasound if necessary, complete blood count.
Retinopathy—dilated ophthalmologic examination
Strokes, aneurysms, moyamoya—brain magnetic resonance imaging/MRA.
AVN—imaging with plain films, magnetic resonance imaging.
Chronic lung disease/asthma—pulmonary function tests.
Iron overload—serial serum ferritins, imaging for hepatic iron.
Red cell alloimmunization—red cell antibody testing; blood bank communication for transient red cell antibodies at all institutions where patient has received blood in the past.

TABLE 4. TRANSFUSION PROTOCOL FOR PREGNANT WOMEN WITH SCD

TRANSFUSION PROTOCOL

Before transfusion
Establish indication (see below):
Select best method for transfusion—simple or exchange transfusion; exchange transfusion should be considered for acute stroke, severe ACS, or major surgery.
Establish post-transfusion haemoglobin and haemoglobin S (sickle haemoglobin) goals—for most SCD-related complications, post-transfusion haemoglobin should be 10 g/dL but not above 12 g/dL in patients with SS; haemoglobin S for SCD-related complications should be 50%.
Obtain red cell antigen genotype or phenotype before transfusion if not obtained previously.
Consider quantitative haemoglobin S post-transfusion as well as pre-transfusion—this may help with monitoring for delayed hemolytic transfusion reactions.
Type and cross match; then, select E-, C-, K-matched units in addition to ABO, D matched; honor transient and present red cell antibodies; for patients with a history of severe delayed hemolytic transfusion reactions or

multiple red cell antibodies, consider extended antigen matching for Kidd, Duffy, MNS, and other blood groups .

Transfuse leuko-reduced irradiated units, because the patient may be a candidate for stem cell transplant.

Cytomegalovirus-negative units are recommended during pregnancy (RCOG).

HbS-negative units are recommended to allow for best monitoring of post-transfusion HbS goals.

Consider quantitative haemoglobin S post-transfusion as well as pre-transfusion—this may help with monitoring for delayed hemolytic transfusion reactions.

Indications for transfusion during pregnancy:

Acute or simple transfusion

Acute complications of SCD, such as stroke, ACS, acute splenic sequestration.

Acute exacerbation of anaemia with illness—decrease in haemoglobin 2 g/dL; this may be owing to ACS, infection, acute splenic sequestration, or multiorgan system failure.

Acute exacerbation of steady-state anaemia—may be because of iron deficiency, renal disease, increase hemolysis.

Chronic transfusions

Established chronic transfusion protocol at time of pregnancy.

Twin pregnancy

Recurrent severe SCD-related complications during the pregnancy; for example, if exchange transfusion is required during pregnancy or simple transfusion, then strongly consider continuing a chronic transfusion protocol for the remainder of the pregnancy.

In particular circumstances—consider in patients for ACS prevention, acute recurrent pain prevention and past pregnancies with known severe complications.

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CHAPTER 14

Surgery

Patients with sickle cell disease (SCD) are referred for surgery at some point in their life time. Surgical complications are more common in patients with SCD compared to the general population due to their increased risk of post-operative acute chest syndrome, infections, vaso-occlusive pain crises and 30-day surgical mortality.[1]

Pre-operative optimization is a multidisciplinary process that involves a haematologist with SCD expertise, an anesthesiologist, transfusion specialist and the surgical team. Failure to appropriately optimize a patient with SCD peri-operatively can lead to complications such as acute chest syndrome, which is associated with an increased risk of death. Adequate counselling, including education of patient about the procedure and awareness of patient's special considerations, can significantly reduce the emotional stress and anxiety about the surgical procedure. With appropriate planning, management and post-operative monitoring, health care providers can increase the likelihood of optimal surgical outcomes.[2]

WHY SHOULD WE DISCUSS THIS TOPIC?

Surgery in patients with SCD is associated with increased risk [3-7]of:

- Sickle-related complications(painful crisis, acute chest syndromes, renal insufficiency, stoke).
- Increased post-operative complications (25-30%).
- Increased peri-operative mortality (1.1%).

Careful pre-operative assessment and judicious peri-operative management are critical in mitigating these risks. Routine surgery should be avoided if patient is febrile and having a painful crisis.

WHAT OTHER CONSENSUS DOCUMENTS/GUIDELINES ARE AVAILABLE ON THIS TOPIC?

There are currently few existing evidence-based guidelines/consensus documents[8-17] related to SCD:

- National Institute for Health and Care Excellence.
- British Committee for Standards in Hematology.
- Sickle cell society.
- UK forum on haemoglobin disorders.
- NHS screening programme.
- Royal College of Obstetrics and Gynaecology.
- US National Institute of Health.
- Association of Anaesthetists of Great Britain and Ireland.

However, only limited data is available from India regarding peri-surgical complications in patients with SCD. In the current review, we discuss pre-operative, intra-operative, and post-operative strategies to optimize patients with SCD undergoing surgery.

LEARNING OBJECTIVES

- To understand the peri-operative strategy for optimizing patients with SCD undergoing surgery.
- To understand common surgical indications, pre-operative assessment and risk stratification of patients with SCD.
- To review the indications for pre-operative transfusion requirement in patients with SCD.
- To understand the options for post-operative pain management and VTE prophylaxis in patients with SCD.

PRE-OPERATIVE ASSESSMENT

Before proceeding for surgery, the treating physician should assess to: [1-2]

- Determine whether all conservative measures have really failed.
- Determine the need for surgical procedure.
- Consider the risks associated with surgery vs continuing with conservative management.
- Explore lesser invasive options.
- Determine whether surgery will allow them to achieve their personal goals and improve the quality of life.

This process should be a shared decision between the patient and health care providers.

The goals of pre-operative assessment are to ensure that the patient is medically optimized for the intended surgery. It is also necessary to estimate the risk of peri-operative complications and to plan for the optimal management of anticipated complications.[2, 18]

Currently, none of the available surgical risk calculators has been validated for patients with SCD. [19-21] During the pre-operative assessment one must ascertain the sickle cell genotype, frequency of crisis and the date of patient's last crisis, average length of hospital stays during crisis, known triggers for crisis, baseline level of activity, baseline opioid use, steady-state haemoglobin and hematocrit, reticulocyte count, and WBC count, as well as history of blood transfusions.

It is essential to assess the patient's peri-operative risk and fitness for surgery and plan anaesthesia accordingly. Surgeries are stratified into risk categories[1] based on their potential for intra-operative blood loss and post-operative complications (ie, low, moderate, or high risk), shown in Table 1.

The patient's history of strokes, acute chest syndrome, obstructive sleep apnea (OSA), adverse reactions to sedation, or recurrent VTE should be documented since these parameters increase the patient's risk of peri-operative complications. Functional capacity is often measured by the ability to perform metabolic equivalent tasks. Patients unable to perform ≥4metabolic equivalent tasks (i.e, climbing a flight of stairs) have an increased risk of cardiac events. [22-23]

PRE-OPERATIVE TRANSFUSION

The primary goal of pre-operative transfusion is to reduce the risk of post-operative complications by increasing the haemoglobin and reducing the percentage of HbS. Patients with SCD are at increased risk of post-operative morbidity primarily related to acute chest syndrome and pain crises and have a higher risk of mortality compared to the general population. Many patients will require pre-operative transfusion to reduce the risk of post-operative complications such as acute chest syndrome and vaso-occlusive pain crises. Pre-operative optimization for patients with SCD often includes simple transfusion or red cell exchange (RCE). Based on available evidence, some experts have concluded that the benefit of pre-operative transfusion is mostly related to increasing Hb rather than reducing %HbS. Although the current evidence supporting pre-operative transfusion is of low quality, the benefits outweigh the harms; therefore, pre-operative transfusion is still recommended. [24-25]

Recently, the Transfusion Alternatives Pre-operatively In Sickle Cell Disease (TAPS) study [26], a multicenter randomized trial of 67 Hb SS and Hb Sβ0 thal patients, found a reduction in clinically important complications in the transfused patients undergoing medium risk procedures (15% vs. 39%, p=0.02). On the contrary, there was randomized trial from Saudi Arabia of 40 SCD patients undergoing cholecystectomy that reported adverse events in immediate post-operative period due to pre-operative transfusions.[27]

A systematic review and meta-analysis of the randomized and observational studies [28] found no difference in peri-operative mortality, vascular, or non-vascular peri-op-

TABLE:1

LOW RISK	MODERATE RISK	HIGH RISK
Dental procedures	Head & neck surgery	Intra thoracic surgery
Ophthalmological procedures	Orthopedic Surgery	Surgeries with prolonged Anaesthesia requirement (>4 hrs)
Hernia	Urologic Surgery	Major vascular surgery
Dilatation & Curettage	Cholecystectomy	Major spine surgery
Wound debridement	Caesarean Section	Neurosurgery
Endoscopy	Splenectomy	Cardiac valve repairs
Superficial tissue biopsy	Appendectomy	Transplant surgeries

TABLE:2 SHOWS THE SUMMARY OF PRE-OPERATIVE TRANSFUSION RECOMMENDATIONS IN SCD PATIENTS

GENOTYPE	Hb(g/dL)	SURGICAL RISK	RECOMMENDATION
HbSS/HbSβ^0 Thalassemia	<9g/dL	Low/Moderate	Simple transfusion/partial exchange/RCE
HbSS/HbSβ^0 Thalassemia	>9g/dL	Low/Moderate	Partial exchange/RCE
HbSC/HbSβ^0/HbSS on Hydroxyurea with elevated HbF without severe phenotype	>9g/dL	Low	No transfusion
HbSC/HbSβ^0 Thalassemia	>9g/dL	Moderate	Partial exchange/RCE
All Genotypes		High	RCE

erative complications between those treated with pre-operative transfusion vs no transfusion strategy. Based on the current studies, it is fair to advocate that transfusion decisions need to be selective and individualized based on the type of SCD, the baseline haemoglobin, the baseline cardiopulmonary reserve, and the risk of the surgical procedure. If a decision to transfuse is made, phenotypically matched blood must be used to minimize the risk of alloimmunization.

In some situations RCE may reduce the risk of acute chest syndrome and pain crisis in patients with genotype HbSS/HbSβ^0, Hb<9 g/dL, or a severe phenotype (characterized as having a history of stroke, recurrent acute chest syndrome, or prior severe post-operative complications) or any person with SCD undergoing high risk surgery. Patients with a severe phenotype are most likely to benefit from achieving a post RCE goal of %HbS<30%.[24] For those with high baseline haemoglobin (above 9 g/dl), perhaps exchange (or partial exchange) transfusion, rather than simple transfusion, should be used to avoid raising the haemoglobin level above 10g/dl. The transfusion plan should be patient-specific and take into account the SCD genotype, baseline haemoglobin, disease severity, risk classification of the surgery, and history of prior surgical complications. [1, 24,29]

INTRA-OPERATIVE PERIOD

The most important factor to consider intra-operatively is to avoid imbalances in volume status, temperature, acid-base balance, blood pressure, and oxygenation, since derangements on above parameters increase red blood cell sickling, which can result in acute organ injury. It can also manifest as a vaso-occlusive pain crisis, as acute chest syndrome, as an acute kidney injury, or even as an ischemic stroke. [1]

Practical strategies to maintain euvolemia include avoiding prolonged fasting prior to surgery without IV fluids, monitoring fluid intake and output, and decreasing IV fluids as soon as patients are able to maintain adequate oral fluid intake. It is essential to avoid extremely cold or hot ambient temperatures pre-operatively, in the operating room, and in the recovery space while using fluid and corrective warming technology aggressively.

CHOICE OF ANAESTHETIC AGENTS

In general, efforts should be made to minimize exposure to hypoxemia, hypercapnia, acidosis, hypothermia and hypovolemia during surgery. Respiratory depressants should be avoided. Intubations are usually performed after paralysis with a short-acting agent. During induction, steps should be taken to avoid breath holding, laryngeal spasm and struggling. The choice of Anaesthetic techniques usually depends upon age, patient's preference, comorbidities and type of surgery.

Theoretically, in regional Anaesthesia there is regional hypoperfusion, venous stasis, and lack of control of ventilation. There is a redistribution of blood flow with increase in capillary and venous oxygen tension in the blocked region, and compensatory vasoconstriction in the non-blocked area with resultant fall in oxygen. [2, 30]

SURGICAL PROCEDURES

Minimally invasive surgical procedures have shown better outcomes in SCD with relatively short hospital stay. Among SCD patients, laparoscopic cholecystectomy and laparoscopic splenectomy are preferred compared to open surgeries. [31-33]

POST-OPERATIVE PERIOD

Post-operative infection is one of the important factors for sickle related complications. It is essential to monitor for post-operative infection regularly. If a patient's temperature is ≥38 °C, he should be investigated for a source of infection with blood and urine cultures, wound inspection, and chest x-ray. If oxygen saturation falls by ≥2% below the patient's baseline or is ≤94%, it is necessary to give supplemental oxygen and evaluate the patient with consideration for post-operative complications such as acute chest syndrome and pulmonary embolism. The evaluation often includes physical examination, arterial blood gas, and chest imaging. [17]

All patients with SCD should use an incentive spirometer post-operatively since this has been shown to reduce the incidence of atelectasis and acute chest syndrome in hospitalized patients with SCD.[34,35]

POST-OPERATIVE PAIN CONTROL

An important issue in the peri-operative management of SCD patients is adequate pain control. The patient's current pain regimen should be reviewed and a post operative pain management plan should be developed, often similar to a patient's usual inpatient acute pain plan and including patient-controlled analgesia. Many adult SCD patients have had multiple exposures to opioids, are often opioid-tolerant, and tend to require large doses of opiates for adequate analgesia. [36]

A combination of long-acting opioids and a short-acting opioid for breakthrough pain often provides adequate relief. Alternatively, continuous administration of pain medications, through the use of patient-controlled analgesia pumps, may be used. Morphine and hydromorphone are the major opioid agonists used for severe pain management in sickle cell patients in the post-operative period. These drugs have no ceiling effect. However, they can cause severe sedation and respiratory depression. Hence, doses should be discontinued or skipped in patients with a respiratory rate <10.[37]

ACUTE CHEST SYNDROME

Sickle cell patients are at risk for acute chest syndrome in the immediate post-operative period. Excessive administration of IV fluids, as well as respiratory sedation from the use of opioid medications and adjuvants, potentiate this risk.

Maintaining adequate ventilation is the best preventive measure. Pre and post-operative use of incentive spirometry is strongly advised. Prompt recognition is important. All the cardinal signs and symptoms may not be present initially. The spectrum of presentation may range from mild, where hypoxia is minimal, to severe acute respiratory distress. Management consists of ensuring adequate ventilation, including the use of mechanical ventilation in severe cases, oxygen administration, bronchodilators, antibiotics, moderate use of analgesia, and judicious hydration.[2]

DEEP VEIN THROMBOSIS PROPHYLAXIS

Sickle cell disease is a hypercoagulable state. Current evidence suggests increased platelet and coagulation activation, even at the patient's basal state. SCD patients have low circulating levels of anticoagulant proteins C and S, moderate thrombocytosis, decreased platelet thrombospondin-1 content, and increased levels of markers of platelet activation. [38-40]

Adequate deep vein thrombosis prophylaxis must be instituted after all major surgeries until the patients are sufficiently ambulatory.

RECOMMENDATION:

Pre-operative Evaluation

1. Pre-operative optimization is a multidisciplinary process that involves a haematologist with SCD expertise, an anesthesiologist, transfusion specialist and the surgical team.
2. Routine surgery should be avoided if patient is febrile and having a painful crisis.
3. Before proceeding for surgery, the treating physician should assess to:
4. Determine whether all conservative measures have really failed
5. Determine the need for surgical procedure
6. Consider the risks associated with surgery vs continuing with conservative management
7. Explore lesser invasive options
8. Determine whether surgery will allow them to achieve their personal goals and improve the quality of life
9. The patient's history of strokes, acute chest syndrome, obstructive sleep apnea (OSA), adverse reactions to sedation, or recurrent VTE should be documented since these parameters increase the patient's risk of peri-operative complications.
10. For those with high baseline haemoglobin (above 9 g/dl), perhaps exchange (or partial exchange) transfusion, rather than simple transfusion, should be used to avoid raising the haemoglobin level above 10g/dl.
11. The transfusion plan should be patient-specific and take into account the SCD genotype, baseline haemoglobin, disease severity, risk classification of the surgery, and history of prior surgical complications.

Intra-operative Period

12. The most important factor to consider intra-operatively is to avoid imbalances in volume status, temperature, acid-base balance, blood pressure, and oxygenation, since derangements on above parameters increase red blood cell sickling, which can result in acute organ injury.
13. Practical strategies to maintain euvolemia include avoiding prolonged fasting prior to surgery without IV fluids, monitoring fluid intake and output, and decreasing IV fluids as soon as patients are able to maintain adequate oral fluid intake.

Post-operative Period

14. Post-operative infection is one of the important factors for sickle related complication. It is essential to monitor for post-operative infection regularly
15. If oxygen saturation falls by ≥2% below the patient's baseline or is ≤94%, it is necessary to give supplemental oxygen and to evaluate the patient with consideration for post-operative complications such as acute chest syndrome and pulmonary embolism
16. All patients with SCD should use an incentive spirometer post-operatively since this has been shown to reduce the incidence of atelectasis and acute chest syndrome in hospitalized patients with SCD
17. Post-operative pain management can be planned, often similar to a patient's usual inpatient acute pain plan and including patient-controlled analgesia.
18. Adequate deep vein thrombosis prophylaxis must be instituted after all major surgeries until the patients are sufficiently ambulatory.

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CHAPTER 15

Newer Drugs

Sickle cell disease, a haemoglobinopathy, is a global health condition affecting millions of people worldwide. It was first described by Dr. John Herrick in 1910.[1] Later, Ingram and colleagues characterized the pathophysiology of sickle cell disease which is caused by sickle haemoglobin resulting from A to T substitution in DNA producing the GAG to GTG codon and replacement of glutamic acid with valine in the sixth position of the Beta S -globin chain. Subsequent genetic studies contributed to a better understanding of the pathophysiology.[2] Major advances occurred in the last decade after discovery of BCL11A, a γ-globin gene repressor, understanding of switch from fetal to adult haemoglobin and approaches for reactivating fetal haemoglobin were considered as possible therapeutic options.[3] Further advancements such as hematopoietic stem cell transplantation, mixed chimerism, gene editing, and genomics have moved the field forward. In recent years (2017-2019), FDA has approved three new medications for management of this disease along with hydroxyurea which remains standard of care for individuals with sickle cell anaemia. [4]Here, we will emphasise on the recent insight on the pathophysiology of sickle cell disease and recently approved disease modifying therapies to manage SCD.

PATHOPHYSIOLOGY

There is a complex mechanism underlying the pathophysiology of sickle cell disease. The A to T substitution in DNA produces the GAG to GTG codon and replacement of glutamic acid with valine in the sixth position of the Beta S -globin chain. De-oxygenated HbS polymerises thereby altering the structure and function of the red blood cells (RBCs) with formation of less flexible, highly adhesive RBCs. Downstream consequences of these changes include microvascular occlusion, leukocyte and platelet activation, and a pathologically altered endothelium as well as a proinflammatory state. The lifespan of the sickle RBCs is reduced to 1/6th of normal due to repeated sickling and unsickling.[6,7,8] The occlusion of blood vessels and chronic hemolyticanaemia are the two hallmarks of the disease. Recurrent episodes on microvascular occlusion lead to painful vaso-occlusive crises.

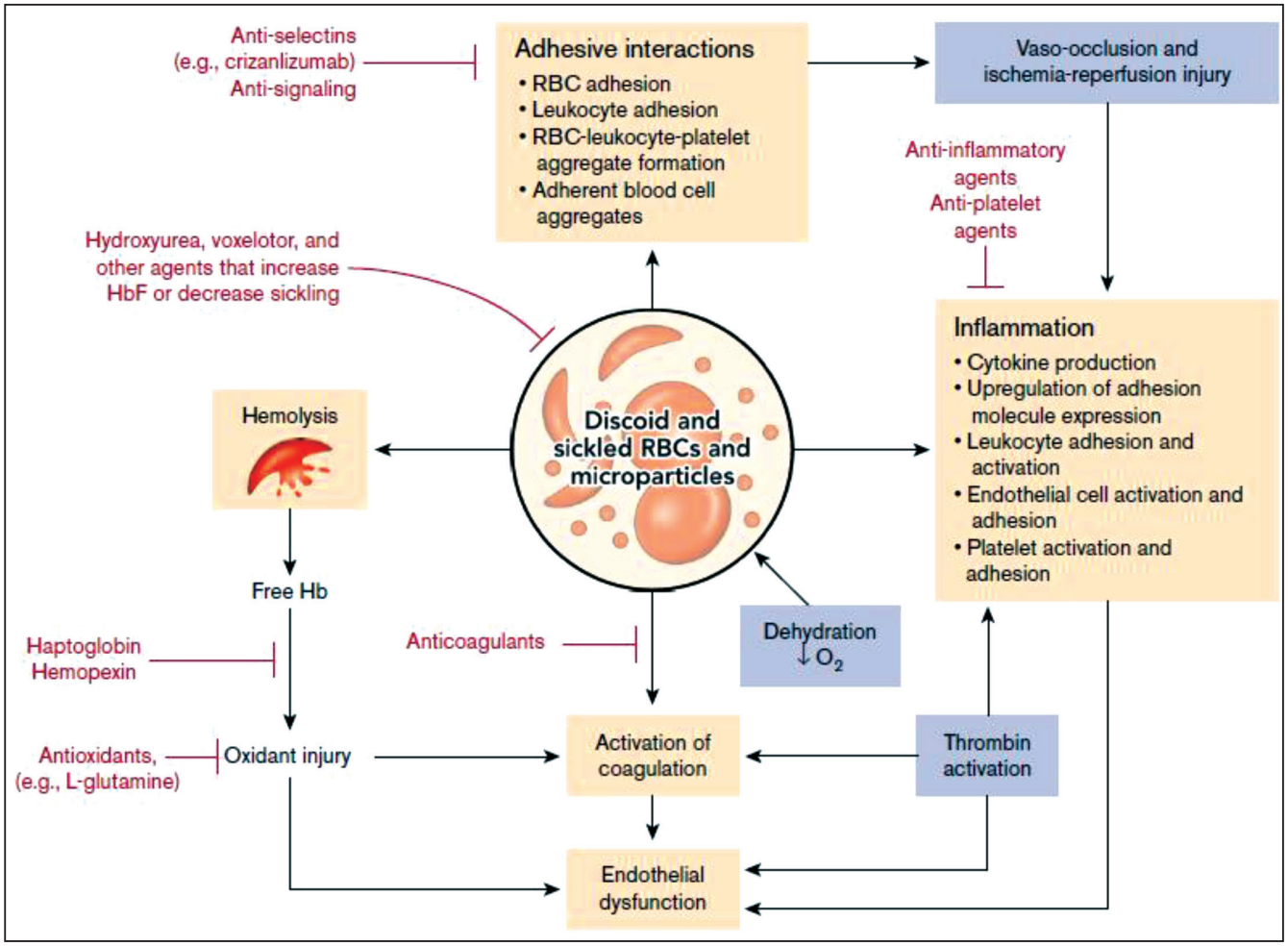
FDA APPROVED DRUGS

L-glutamine- In sickled erythrocytes, there is a decreased ratio of NADH to total NAD as compared to normal, due to an increase in total NAD.[9] The mechanism of action is based on targeting glutamine depletion which has been implicated in red blood cell membrane damage and adhesion. Pharmacological supplementation of L-glutamine was considered in sickle cell disease as glutamine is a precursor of NAD and improves NAD redox potential. Nihara et al in 2014 performed the first controlled trial on L glutamine in sickle cell anaemia.[10] In this trial, oral L-glutamine 0.3 g/kg twice daily up to a maximum dose of 30 g/d was given for 48 weeks. Results of the study showed, decrease in number of vaso-occlusive painful events, substantial increase in NADH and NAD redox potential, without any change in Hb concentration.[11] FDA approved L-glutamine oral powder (Endari, Emmaus Medical, Inc.) in July 2017, for oral administration for adult and pediatric patients older than 5 years of age after a randomized, double-blind, placebo-controlled, multi-center clinical trial (NCT01179217) showed fewer hospitalizations due to acute pain crisis, decreased cumulative hospital days, lesser an incidence of acute chest syndrome. The dose recommended is 10-30 grams orally twice daily.[12] Each dose is to be mixed with beverage or food before ingestion. The common adverse reaction included gastrointestinal side effects such as nausea, constipation, abdominal pain as well as headache, cough, pain in extremity, back pain, and chest pain. Less common side effects also included hypersplenism, abdominal pain, burning sensation, hot flashes.[13,14] L-glutamine has been approved for all types of sickle cell disease, but the study included only HbSS patients. The Genotype-specific subgroup analyses, cost or

feasibility are yet to be studied.

Crizanlizumab (ADAKVEO): It is a humanized monoclonal antibody that binds to P-selectin, blocks the adhesion of activated erythrocytes, neutrophils, and platelets by interacting with ligands of P selectin. [15,16] In July 2008, this compound was given an orphan drug designation. [17,18] FDA approved ADAKVEO (crizanlizumab-tmca) on November 15, 2019, based on a phase 2, multicenter, randomized, placebo controlled double blind study (SUSTAIN study) (NCT01895361).[19] It was shown to reduce the frequency of vaso-occlusive crises in adult and pediatric sickle cell disease patients aged 16 years and older. The recommended dosage is 5 mg/kg administered intravenous infusion over 30 minutes at Week 0, Week 2, and every 4 weeks afterwards. It can also be used along with hydroxyurea.[20] Vaso-occlusive crisis events as well as time to first vaso-occlusion were significantly decreased in the crizanlizumab arm compared to placebo. The major difference was seen in non HbSS subgroup and those receiving concomitant hydroxyurea therapy. The adverse events reported in 10% of patients included nausea, vomiting, diarrhoea, pruritis, arthralgia, back pain, pyrexia while a few suffered from acute chest syndrome, pneumonia, intracranial bleed, thrombosis, ventricular failure, sepsis.[21] The STAND trial, another phase III trial is ongoing for evaluation of safety and efficacy crizanlizumab, in adolescent and adult patients (> 12 years) with sickle cell disease. SOLACE, STEADFAST and SPARTAN trials are amongst the other ongoing trials of

SUMMARY OF NEWER DRUGS[27]



Crizanlizumab for VOCs and other indications in sickle cell disease.[22,23]

Voxelotor: Also known as Oxbryta, binds to the N-terminus of alpha subunit of HbS, stabilizes the oxygenated haemoglobin state thereby reducing sickling.[24] Oxbryta (GBT440) was FDA approved on November 25, 2019 for both adults and pediatric patients 12 years of age and older. The HOPE (NCT 03036813), a randomized, double-blind, placebo-controlled, multicenter trial, evaluated efficacy of this drug in 274 patients and showed an improvement in haemoglobin levels and reduced hemolysis.[25] Randomisation was done among 274 patients to Voxelotor 1500 mg (N=90), 900 mg (N=92), or placebo. The primary efficacy outcome was defined as Hb increase of >1 g/dL from baseline to week 24. The response rate for Voxelotor was 51.1% in comparison to 6.5% in the placebo group. Additional efficacy evaluation included significant improvements in change in Hb, indirect bilirubin and reticulocyte count. The most common side effects encountered included fatigue, pyrexia, headache, nausea, diarrhea, abdominal pain in >10 % cases. The recommended dose is 1500 mg orally once daily with or without food. Other studies are going on regarding Voxelotor use in Pediatric and adult (12-65 years) population with sickle cell disease.[26]

OTHER AGENTS IN PIPELINE

Besides these FDA approved drugs, there are various novel agents based on different mechanism of action which are being studied for sickle cell disease. The agents targeting adhesion includes Rivipansel, IVIg, Savuperin which acts by either selectin inhibitor or disrupts neutrophil mediated sRBC capture.[28, 29] Others like arginine, citrulline, N acetylcysteine, omega3 fatty acids act by preventing inflammation by reducing oxidative stress and decreased formation of reactive oxygen species.[30, 31] Novel agents are being studied for inducing HbF includes Decitabine, Metformin among others.[32, 33] Antiplatelets, anticoagulants like Rivaroxaban, Apixaban, unfractionated Heparin are also being studied.[34, 35] Novel opioid sparing agents are in trials for managing painful crisis including Buprenorphine, Ketamine, gabapentin, momentin.[36, 37]

RECOMMENDATION:

The FDA approved newer drugs for sickle cell disease had different mechanisms of action than hydroxyurea and have minor adverse effects. These drugs can be considered along with hydroxyurea as a possible option to reduce complications in sickle cell disease. Adherence to disease modifying therapies is important to reduce complications related to SCD. Availability of these newly approved therapies remains a constraint especially given high expenses associated with these drugs compared to the conventional drugs like hydroxyurea. In the pandemic era of COVID 19, Crizanlizumab may be beneficial in reducing the number of hospital visits associated with VOCs. Reduction in the cost of these newer drugs may lead to increased use as treatment options for sickle cell disease.

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CHAPTER 16

Food And Nutrition

While management of Sickle Cell Disease is largely driven by medication and blood transfusion, the role of nutrition has been grossly underestimated in tackling the disease. There is substantiated data on the high incidence of stunting and underweight in general sickle cell patients published by African authors.[1, 2]

In 1985 already a group from the US reported an improvement in the clinical course of sickle cell crisis in children by enteral nutrition through a nasogastric tube. In this experience, it was the substitute of calories which made the difference.[3] The lower intake of calories may be caused by reduction of appetite and the need of higher energy uptake in SCD.

In a publication from Jamaica about nutrition and sickle cell disease[4], the author summarised: In SCD there is

- Inapprotriate low energy uptake due to appetite suppression by inflammatory mediators.
- Elevated energy expenditure related to physiological adaptations to hemolysis.
- changes in body composition resulting in a relative increase in visceral FFM.
- inflammation.

The study observed that the difference in weight and height increases with age and is more pronounced in men than in women.[1,4] In one publication from Tanzania, it was correlated with hospitalisation but not with mortality in an urban setting.[5] This may be different in rural settings.

The consequence of these data is: **Sickle cell patients need more energy intake than normal people in all ages**.[6]

FLUID INTAKE

Dehydration increases the concentration of sickle cell hemoglobin in red blood cells along with the risk of vaso-occlusive crisis. There are studies from the US reporting a reduced intake of fluids and higher intake of sodium in sickle cell children compared to healthy individuals.(10) It has also been demonstrated that the sickle cell patients may have lost the capacity of concentrating the urine even in a situation of dehydration. (11) Even though these observation have not been reported from India, adequate intake of clean water is essential to prevent vaso-occlusive crisis.

VITAMINS AND MICRONUTRIENTS

There is an increased need for vitamins and micronutrients in sickle cell disease. Several studies have shown that supplementation of different vitamins improve the clinical status of SCD patients.[6] Others even have anti-sickling activity like vitamin C, A and E, zinc, copper and magnesium.[6a] Omega3 fatty acid seemed to reduce the adherence of red blood cells to the endothelium and reduced the incidence of occlusive crisis.[6,7] Substitution of folate, though included in the general therapeutic procedure, has only low evidence according to a Cochrane review of 2018, as only one randomised study met the inclusion criteria of the analysis.[7a]

What does this mean for dietary proposals for sickle cell patients, especially in rural areas? The could make use of Moringa tree, its leaves and pods, containing protein, vitamins, special aminoacids and many more ingredients. (8) Another choice is nuts, specially peanuts offering protein, carbohydrates and fat.[9]

Vitamin D deficiency has been observed in many sickle cell disease patients. The incidence is higher compared to healthy subjects.[12] These data are not from India, but vitamin D deficiency in India is widespread.[13] Main source of vitamin D is sunlight exposure. General food rarely contains vitamin D except fish and in lesser amount milk. In a study from the US, it was seen that sickle cell patients with low vitamin D levels experienced higher hospitalisation rates. This corresponds to the difference between those who never vs. often had fish, cheese, milk or egg in their diet.(12) A Cochrane review looked at the substitution of vitamin D deficiency, but they found only a low evidence.[14] Still, in sickle

cell disease, exposure to sunlight and foodwith Vitamin D should be suggested to patients.

The aminoacid arginine has gained special interest in the recent years. It has played an important role in many diseases. One of its actions is the production of nitrid oxide leading to a relaxation of blood vessels. The alteration of endothelial function is linked to diseases of the cardiovasular system like hypertension, diabetes, arterioskleosis. [15] Low global arginine bioavailability (GAB) leads to severe complications on sickle cell disease.[16] A randomised study in a small number of children admitted for severe pain showed a marked reduction of opioid use in children treated with arginin 100 mg TID.

Arginin is available in peanuts, pumpkin seeds, milk, cheese and curd, chicken leg, oats and corn.[17]

TREASURE OF TRADITIONAL KNOWLEDGE

Many publications of laboratory studies following experience of traditional healers have been able to demonstrate anti-sickling activity of plants as well as the ability to reverse anti-sickling in sickled cells of patients. These are publications about **Ocimumbasilicum** (Tulsi)[18,19], **Curcuma longa** (Turmeric)[20], a mixtire of **papaya and sorghum bicolor** (great millet).[21] **Moringa leaves**[21a, 21b] had anti-sickling activity as well as **fermented Moringa leaves.**[21c]

After a short report about dramatic improvement in a 7-year-old patient [21d] after intake of **fermented raw papaya** in 1987, a publication in 2006 confirmed the results of laboratory tests.[21e] No further research has been published on this topic. Another publication reports the anti-sickling effect of papaya leaves.[21f] Onion and garlic as well have demonstrated anti-sickling activity.[21g] as well as **neem seed oil.**[21h]

Sorghum bicolor, a medicinal plant from Nigeria registered with the FDA, showed a reduction of intra-cellular hemoglobin in patients after four weeks intake in a randomised study. Clinical effects were not looked at due to the short treatment time.[22]

Cajanuscajan (Pigeon pea) has been tested in Ciclavit, a herbal medicine from Nigeria.[23] A randomised placebo controlled study in 100 patients over 6 months showed a reduction in hepatomegaly in the study group compared to an increase in the control group. The incidence of painful crisis was stable in the study group but increased in the control group. Though the Cochrane analysis of the studies with the two herbal medicines from Nigeria led to a low incidence[24], these vegetables may have a protective effect and should be included in every days meals.

After a publication of in-vitro anti-sickling activity[25] and experience from a late healer, a nurse interested in traditional medicine started to treat sickle cell patients in her area with a tonic consisting of aloe vera and jaggery. After taking the herbal medicine, symptoms stopped in patients within 7 to 10 days and most of them could live a normal life. Though there are more than 250 patients treated, this expereince is not published.

RECOMMENDATION:

1. Sickle cell patients need a higher intake of energy, protein, carbohydrates and fat.
2. Higher intake of fluid compared to healthy subjects is important to prevent sickle cell crisis.
3. Substitution of folic acid and vitamin D and vitamin D should be given despite low evidence level.
4. Food should be chosen according to the need of vitamins and micronutrients as presented.
5. Plants, vegetables, fruits that have proven anti-sickling activity in the lab or in clinical reports should be part of daily food.

Table 1 Dietary reference intakes for healthy individuals and dietary sources of nutrients suggested for nutrition management of SCD[a]

Nutrient	Increased Need in SCD	DRI (RDA) Children	DRI (RDA) Adults	Dietary Sources
Protein (g/d)	✓	1–3 y 13 4–8 y 19 9–13 y 34 14–18 y F 46 14–18 y M 52	19 –70+y F 46 19 –70+y M 56 Pregnancy 71 Lactation 71	Beans, Peas, Lentils, Nuts, Seeds, Peanut, Butter, Whole Grains, Meat, Fish, Poultry.
Carbohydrate (g/d)	✓	1–18 y 130	19–70+ y 130 Pregnancy 175 Lactation 210	Wheat, Rice, Oats, Sorghum, Millet, Fonio Corn, Quinoa, Beans, Lentils, Peas, Potatoes, Fruits, Vegetables, Breakfast Cereals, Breads, Pasta
Omega 3 Fatty Acids α-Linolenic Acid (g/d)	✓	1–3 y 0.7 4–8 y 0.9 9–13 y F 1.0 9–13 y M 1.2 14–18 y F 1.1 14–18 y M 1.6	19–70+y M 1.6 19–70+y F 1.1 Pregnancy 1.4 Lactation 1.3	* α-Linolenic Acid sources; Walnuts, Flaxseeds, Chia seeds, Black Walnuts, Edamame
Dietary Fiber (g/d)		1–3 y 19 4–8 y 25 9–13 y F 26 9–13 y M 31 14–18 y F 26 14–18 y M 38	19–50 y M 38 19–50 y F 25 51–70+ M 30 51–70+ F 21 Pregnancy 28 Lactation 29	Whole grains (wheat, millet, sorghum, fonio brown rice), lima beans, kidney beans, black beans, pinto beans, black-eyed peas, sweet potatoes, greens pistachios, almonds, banana, apples, pears, berries, avocado, yams
Vitamin B6 (mg/d)	✓	1–3 y 0.5 4–8 y 0.6 9–13 y 1.0 14–18 y F 1.2 14–18 y M 1.3	19–50 y 1.3 51–70+ M 1.7 51–70+ F 1.5 Pregnancy 1.9 Lactation 2.0	Chickpeas, Bananas, Potatoes, Fortified Breakfast Cereals, Tuna, Salmon, Turkey
Vitamin B12(μg/d)	✓	1–3 y 0.9 4–8 y 1.2 9–13 y 1.8 14–18 y 2.4	19–70+y 2.4 Pregnancy 2.6 Lactation 2.8	Clams, Liver, Fortified Cereals, Fortified Nutritional Yeast, Rainbow Trout, Salmon, Tuna
Folate (μg/d)	✓	1–3 y 150 4–8 y 200 9–13 y F 300 9–13 y M 400 14–18 y 400	19–70+y 400 Pregnancy 600 Lactation 500	Black-eyed Peas, Chickpeas, Asparagus, Avocado, Spinach, Broccoli, Brussel Sprouts, Wheat Germ, Enriched Pasta, Mustard Greens, Kidney Beans
Vitamin A (μg/d)	✓	1–3 y 300 4–8 y 400 9–13 y 600 14–18 y F 700 14–18 y M 900	19–70+y M 900 19–70+y F 700 Pregnancy 770 Lactation 1,300	*Beta—carotene sources Sweet Potato, Carrots, Cantaloupe, Broccoli, Spinach, Pumpkin, Mango, Red peppers, Sweet Potatoes, Papaya
Vitamin C (mg/d)	✓	1–3 y 15 4–8 y 25 9–13 y 45 14–18 y F 65 14–18 y M 75	19–70+y M 90 19–70+y F 75 Pregnancy 85 Lactation 120	Broccoli, Oranges, Kiwi, Guava, Strawberries, Collard Greens, Lemons, Brussel Sprouts, Cauliflower, Bell Peppers, Tomatoes, Apples
Vitamin D (μg/d)	✓	1–3 y 15 4–8 y 15 9–13 y 15 14–18 y 15	19–70 y 15 >70 y 20 Pregnancy 15 Lactation 15	Salmon, Tuna, Mackerel, Cod liver oil, Sardines, Fortified Cereals, Fortified Milk & Yogurt, Fortified Soy Milk, Eggs, Fortified Orange Juice, Mushrooms

Table 1 (Continued).

Nutrient	Increased Need in SCD	DRI (RDA) Children	DRI (RDA) Adults	Dietary Sources
Vitamin E (mg/d)	✓	1–3 y 6 4–8 y 7 9–13 y 11 14–18 y 15	19–70+y 15 Pregnancy 15 Lactation 19	Wheat germ oil, Sunflower Seeds, Almonds, Spinach, Broccoli, Plant Oils, Peanut Butter, Spinach
Calcium(mg/d)		1–3 y 700 4–8 y 1,000 9–13 y 1,300 14–18 y 1,300	19–70 y M 1,000 19–50 y F 1,000 51–70+y F 1,200 >70 y M 1,200 Pregnancy 1,000 Lactation 1,000	Yogurt, Cheese, Sardines, Milk, Fortified Soymilk, Calcium-set Tofu, Fortified Cereals, Turnip Greens, Kale, Fortified Orange Juice, Salmon with bones, Frozen Yogurt, Ice Cream
Magnesium (mg/d)	✓	1–3 y 80 4–8 y 130 9–13 y 240 14–18 y F 360 14–18 y M 410	19–30 y M 400 31–70+y M 420 19–30 y F 310 31–70+y F 320 Pregnancy 350 Lactation 320	Almonds, Cashews, Peanuts, Spinach, Whole Wheat Cereal, Soymilk, Black Beans, Oatmeal, Avocado, Dark Chocolate, Edamame, Baked Potato with Skin, Brown Rice, Kidney Beans
Potassium (mg/d)		1–3 y 3,000 4–8 y 3,800 9–13 y 4,500 14–18 y 4,700	19–70+y 4,700 Pregnancy 4,700 Lactation 5,100	Sweet Potato, Cantaloupe, Watermelon, Okra, Pineapple, Beans, Banana, Orange, Collard Greens, Potatoes, Black-eyed Peas, Okra, Peanuts, Peaches, Tomatoes, Beets
Zinc (mg/d)	✓	1–3 y 3 4–8 y 5 9–13 y 8 14–18 y F 9 14–18 y M 11	19–30 y M 400 31–70+y M 420 19–30 y F 310 31–70+y F 320 Pregnancy 350 Lactation 320	Oysters, Crab, Beef, Fortified Cereals, Chickpeas "Hummus", Oatmeal, Beans, Lentils, Almonds, Cashews
Selenium (µg/d)	✓	1–3 y 20 4–8 y 30 9–13 y 40 14–18 y 55	19–70+y 55 Pregnancy 60 Lactation 70	Brazil nuts, Tuna, Sardines, Shrimp, Brown Rice, Wheat Bread, Oatmeal, Baked Beans, Oatmeal, Spinach
Dietary Flavanols				*Quercetin sources Cherries, Blueberries, Cranberries, Black currants, Elderberries, Goji berries, Chokeberries, Juniper berries, Black-eyed Peas, Red Onions, Okra, Watercress, Capers, Black Diamond Plums, Brussel Sprouts, Cilantro, Fennel leaves, Ancho peppers, Radicchio, Chia seeds, Carob, Buckwheat, Kale, Dill
Dietary Nitrates				Spinach, Lettuce, Beetroot, Celery, Chinese Cabbage, Turnips, Endive, Leeks, Kohlrabi, Fennel, Dill, Parsley
Dietary Antioxidants and Phytochemicals				Cloves, Cinnamon, Vanilla Beans, Oregano, Thyme, Sage, Rosemary, Tumeric, Black Raspberries, Blueberries, Cranberries, Black Currants, Elderberries, Blackberries, Strawberries, Pomegranates, Apples

Notes: *DRIs provided for normal requirements. ✓Increased need for SCD.

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Abbreviations: ALT, alanine amino transferase; AST, aspartate amino transferase; ALP, alanine phosphatase; β^{th+}, beta thalassemia; CRP, c-reactive protein; DRI, dietary reference intakes; HbSS/SCA, sickle cell anemia; HbSC, hemoglobin SC; HU, hydroxyurea; IL-6, interleukin-6; IU, international units; RDA, recommended dietary allowances; RMR, resting metabolic rate; REE, resting energy expenditure; SCD, sickle cell disease; S20, sickle mice fed 20% protein; S35, sickle mice fed 35% protein; TB, total bilirubin; F, female, M, male.

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CHAPTER 17

Prevention And Control

Sickle cell disease (SCD) is the most common inherited disorders of haemoglobin. In SCD, substitution of a single amino acid glutamic acid with valine at the 6th position due to a point mutation (A→T) in beta globin (β-globin) gene results in sickle haemoglobin (Hb S), which has tendency to polymerize inside the red blood cells (RBCs) under hypoxic condition. Surprisingly, the Indian SCD patients have high fetal haemoglobin (Hb F) associated with Arab Indian/Asian haplotype, which is supposed to have a milder clinical phenotype.[1] SCD is an autosomal recessive disease inherited from one generation to the next. There are two forms of SCD based on the number of faulty sickle genes (Hb S) that are recessively inherited from parents (i) Sickle cell trait/carrier (Hb AS): persons having only one sickle gene ($\beta^A\beta^S$) out of the two alleles acquired from either parent is known as a sickle cell carrier/trait. These people are usually asymptomatic and do not require treatment, but they may pass on the sickle gene (β^S) to their children. (ii) Sickle cell homozygous (Hb SS): sickle cell homozygous (Hb SS) or sickle cell illness refers to people who have two sickle genes ($\beta^S\beta^S$) in alleles inherited from both parents.

SCD has become a major public health concern in developing countries like India, which is a second largest hub for SCD after South Africa, estimated to have approximately 33,900 [CI: 15,900–64,700]) newborns with SCD by the year 2050[2]. In India, the first case of SCD was identified in 1952, in a tribal population, living in the Nilgiri hills of south India.[3] Over the last few decades, SCD has marked its presence pan India with a varying degree of prevalence in different ethnic group.[4] However, states such as Gujarat, Maharashtra, Madhya Pradesh, Chhattisgarh, Odisha, Jharkhand and Telangana are the states with high prevalence of SCD in India.[4,5]

- India has the main reservoir of Hbpathies like SCD and Thalassemia in the entire world, whose prevalence is high and varies from 5 to 30% depending on the geographical area. It has a huge socio-economic burden and contributes significantly to IMR and MMR and anaemia.
- SCD, Thalassemia and haemoglobin diseases are three major HbPathies seen in different parts of India. Recently, GoI and all State govts are committed to provide all health care facilities free of patients to patients irrespective of location or status.
- Rs 2 lakhs per patient per year is being spent from the govt exchequer towards the management.
- Thus, a control of HbPathy is utmost essential.
- For logistic and financial realistic point of view, it is imperative to integrate all types of Hbpathy in one programme as the patients, the blood sample, the equipment and human resources are the same.

GOAL

- 5% reduction of SCD (HbSS) and other HbPathies (disease) in 5 years.
- Consolidation and futher reduction in subsequent years.

METHODOLOGY OF PREVENTION & CONTROL:

- Prevention of birth of the major HbPathies including SCD (HbSS).

a) By antenatal screening and counselling to avoid marriage among two carriers.

b) Prenatal diagnosis with selective termination of the pregnancy if the foetus is found to suffer from major Hb Pathy.

- Curative option: Allo-genic Bone Marrow Transplantation.
- Holistic optimal assessable healthcare system to all: This will reduce the morbidity and mortality. Ensure the normal life expectancy, excellent QoL and compliance.
- Gene therapy: Curative option which may be realistic in future.

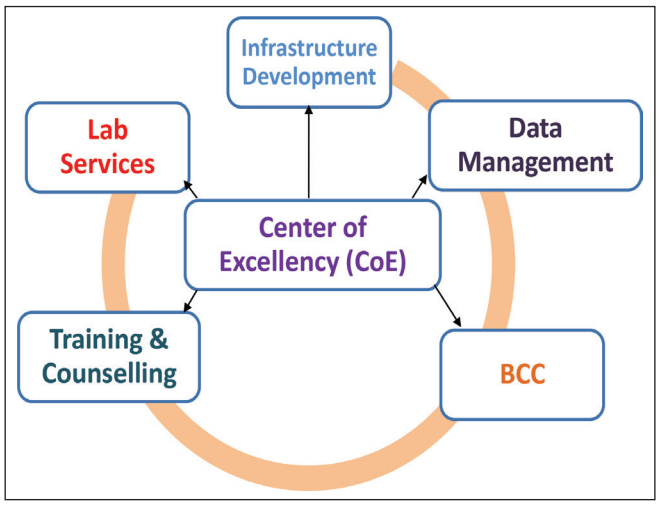
CORE COMPONENTS OF CONTROL PROGRAMME

PRINCIPLE

- A Central body has to be in charge.

PRIORITY GROUPS FOR SCREENING

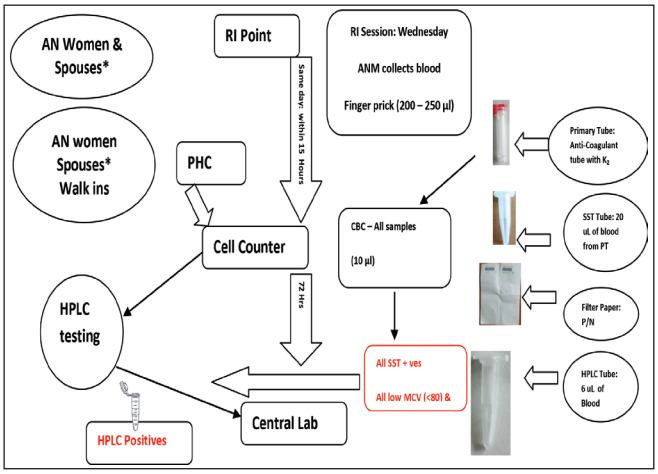
SL NO.	PRIORITY GROUP	POINT OF SCREENING
1	Antenatal women	Periphery – RI centers/PHC/CHC*
2	Spouses of AN women (positives)	Periphery – RI centers/PHC/CHC*
3	High school children (2^{nd} year onwards)	Schools & CHCs*
4	Walk-ins (includes eligible couples and college goings)	CHCs*
5	All population in due course	CHCs* / Hospitals
CHCs: Approximately 4 CHCs in each District*		



- Zonal headquarters in every state.
- CoE (2-4 in every state).
- State can modify the framework as per the need and situation.
- Work flow.
- Screening test at peripheral level which should be reasonable and sensitive for SCD, Beta-Thal and HbE.
- Positive samples should be carried to DHH for confirmation by HPLC/CapZone Electrophoresis. Controversial cases should be referred to CoE.
- Every DHH should work as a nodal centre for providing diagnostic and therapeutic facilities along with managing complicated cases and imparting training to all the health professionals from time to time.
- One uniform training, management and other related modules should be created by ISHBT/ICMR/other stakeholders which should be followed across the country. This will help in data analysis and future interventions.
- PND facilities should be available across every state so thata pregnant female can easily access free of cost.
- BMT facilities should be available in one to two centre at least in every state.
- Counselling/Awareness/vocational rehabilitation.
- Data system.
- Every person included in the programme should be included in the centralised data system with bar code facilities.
- Analysis of the data should be done inside the State and at national level once in a year or as per need.

SPECIMEN AND DATA FLOW

ROLE OF HEALTHY FUNCTIONARY: ANM



- Sample collection and handing over to Courier.

- Record keeping in register and Tab.

COURIER

- Sample collection logistics delivery.
- Sample receiving and transport to ILR point/Cell Counter site.

LAB TECHNICIAN

- Sample receiving and checking sample status.
- Testing and reporting.
- Handing over to courier for sending to HPLC/ACZE lab.

DATA MANAGEMENT

Data management system with Apps and other requirements should be developed by Govt. of India or State Govts. depending on the need.

TYPES OF TRAINING

1. State level Training.
2. Regional level Training.
3. District level workshop Training.
4. District level TOT training.
5. Block level health worker M and F training.
6. Sector level ASHA orientation.

TRAINING PARTICIPANTS

1. State level Training- All CDMOs.
2. Regional level training- All MOs.
3. District level workshop training- All DPMU staffs ,MOIC and BPM.
4. District level TOT training- BDM,LT,Counsellor and LHV/ Staff Nurse.
5. Block level Training- All HW (M), HW (F) and Other staffs.
6. Sector level Training-All Sector level ASHA.

ROLE OF HEALTHY FUNCTIONARY: MO IN-CHARGE/BLOCK PROGRAMME MANAGER

- Participant in district level orientation.
- Selection of block level functionary for ToT.
- Will monitor the quality aspect of trainings down the line.

BLOCK DATA MANAGER

- Participant in district level orientation.
- Master trainer of sample collection in block level trainings.

LAB TECHNICIAN

- Participant in district level orientation.
- Master trainer of sample collection in block level trainings.

ANM

- Ensuring 100% participation in ANM orientation.

DISTRICT ACCOUNT MANAGER/ BLOCK ACCOUNT MANAGER

- Timely submission of UC-SoE.

MONITORING-OUTCOME INDICATORS

INDICATOR	SOURCE	FREQUENCY
Number of ANC women registered	ANM / Database	Monthly
Number of ANCs (pregnant woman or her partner) registered & tested before 16 weeks	ANM / Database	Monthly
Number of ANCs (pregnant woman or her partner) registered & tested before 16 weeks	ANM / Database	Monthly
Number of eligible couples who know their MHD status before their 16 weeks	ANM / Database	Monthly
Number of eligible couples where both partners are known to be carriers accept PND	ANM	Monthly
Proportion of homozygous pregnancies where the couple opted for MTP	Project database	Annually
Number of individuals who walk-in to know whether or not they are carriers	Project database	Quarterly

IEC / BEHAVIOUR CHANGE COMMUNICATION

Objective

- To remove stigma.
- To make it a part of existing programme.
- Community level ownership.
- Multi-Sectoral Convergence for supportive supervision.

Monitoring & Evaluation: Should be designed by Govt. of India / State Govts as per the need.

As an template for monitoring and evaluation of ante-natal females and school going children -

MONITORING PROGRAMME MANAGEMENT

INDICATOR	SOURCE	FREQUENCY
No. of schools reached by camps in the month in the district*	District Coordinators	Monthly
No. of school children screened	District Coordinators	Monthly
No. of colleges visited where information sessions were held	District Coordinators	Monthly
No. of college students reached at information sessions	District Coordinators	Monthly
No. of street plays reported to have been done	Media group	Monthly
No. of street plays attended by the project staff to judge quality	District Coordinators	Monthly

*** From 2nd year of programme launch**

Impact Indicator: Before Programme as baseline data and during / after programme for monitoring of effectiveness.

- Prevalence of major haemoglobinopathies at birth.

SENTINEL SURVEILLANCE CENTRES

➢ All births will be monitored at major hospitals by genetic analysis for major haemoglobin disorders.

MONITORING PROGRAMME MANAGEMENT

INDICATOR	SOURCE	FREQUENCY
Number of Children born with SCD or TM or HbE Major	Sentinel Surveillance Centres	Monthly

RECOMMENDATION:

1. Prevention and Control of SCD along with other HbPathies is cost-effective and beneficial.
2. SCD should be integrated with thalassemia, and HbE disease in government programmes considering the fact that it involves the same population, same impact and same logistics.
3. Considering the magnitude of problem in India, one screening test which can reasonably capture major HbPathies like SCD, Thal and HbE disease may be initiated at community level followed by confirmation at referral lab at district level. POC equipments needs to be examined from all the angles before its use in govt programmes.
4. HbPathies are associated with anaemia in significant percentage of cases. Thus, the Taskforce unanimously feels that the national anaemia programme should be integrated with HbPathies programmes.
5. Affordable and accessible holistic health care system will improve the morbidity and mortality, and regain the confidence of SCD community. This will help in eradicating the social stigma which is essential for effectiveness of any control programme.

6. This guideline has outlined the framework of control and prevention programme. However, the Government of India/State governments should formulate their programmes considering their specific needs.
7. The data system should be robust and secured. It can be integrated to create a national database.

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CHAPTER 18

Research Needs: Priorities & Strategies

Sickle Cell Disease (SCD) is the commonest genetic blood disease which is widely prevalent across the globe with variable distributions, phenotypes, complications and life expectancy, etc.[1] There is a greatest dichotomy between the science (single Amino acid mutation at 6th Position of beta globin chain of Hb in all cases) and huge variability in clinical presentation and this mystery needs to be unfolded. The standard concepts based on research are mostly derived from haplo types like Senegal, Bantu and Benin, which may not be true in the case of the Arab-Indian haplotype prevalent in our country.

Although a considerable number of studies were carried out in India, they are mostly limited to screening, and some are extended to molecular typing of HbS. Very few clinical and interventional studies are available. The Indian studies available so far have very fewer implications on practice, particularly in the prevention and management of the disease.[2] Thus there is a huge unmet medical need which urgently requires addressing with research, as outlined below.

• EPIDEMIOLOGY

- Screening/Surveillance/Registry/Understanding the natural history.

Initially, SCD was supposed to be prevalent in malaria-endemic zones affecting more people in tribal and rural areas. But this scenario has been completely changed due to population migration and marriage across the castes.[3] The Malaria epidemiology in India has also changed significantly due to mutation in the malaria parasites as well as environmental changes due to developmental activities. This situation has also impacted the overall survival of SCD due to better nutrition, healthcare facilities and improved living conditions. Thus the current epidemiology and the natural history of SCD should be ascertained by well-planned population-based research across the country.

Screening for SCD, preferably from an early age, is necessary, and these cases are to be followed with the required care. Registries and surveillance systems in the public health system hold great promise in providing essential information on the SCD patient population. Data collected through these systems often provide insights into populations receiving interventions or care under the programme and to understand the outcomes of such interventions and programmes.

Screening methods suitable to the population are to be established. Efforts to establish surveillance and registries using information technology are to be made. Later these systems are to be standardized and scaled up at the national level for the use of the national SCD programme.[4] **(*Please see the Chapter on Screening and Diagnosis Laboratory Testing of SCD*)**

• IMMUNIZATION/ANTIBIOTIC PROPHYLAXIS

The benefit of these two modalities in improving the outcome was established in African countries where the prevalent haplotypes are not Arab-Indian. Thus the advantage of a specific immunization and antibiotic prophylaxis in Indian patients needs to be validated in the present prevalent situation. Hence, more intervention studies addressing this objective are required.

(*Please see the Chapters on Immunization in SCD and Management of SCD in Stable Condition*)

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• CLINICAL RESEARCH

The clinical presentation varies according to the HbS haplotype. Hence, the Indian SCD patients with the Arab-Indian haplotype need to be studied more to ascertain the above parameters. No work has been done in India in this regard. Hence, understanding of the clinical variability by various HbS phenotypes and, more specifically, the complications in pulmonary, cardiac and neurological is required.

(***Please see the Chapters on Management of SCD in Stable Condition, Newer Drugs in SCD& Vaso-Occlusive Crisis Acute Pain***)

Markers of end-organ damage needs to be studies and corroborated.

• TREATMENT / MANAGEMENT

Few studies are available in India regarding the treatment and management of SCD. This small number of studies does not match the huge burden of SCD in India. Hence, it is imperative to undertake studies on the following issues, to guide the programme and practice in India. In addition, standard treatment protocols are to be developed for routine management and complications. This kind of protocol is primarily helpful to doctors working in peripheral primary health care facilities (***Please see the Chapters on Management of SCD in Stable Condition, Efficacy of Hydroxyurea Therapy in Indian SCD patients& Vaso-Occlusive Crisis Acute Pain***).

For the following issues, some information is available in the global literature. However, Indian-specific information is scanty. Hence, there is a need of undertaking research among Indian SCD patients.

- Developing standardized treatment protocol.
- Iron Overload / Iron Chelation / Iron Deficiency(*Please see the Chapters on Assessment of Iron Overload and Chelation Therapy in SCD*).
- Red cell antigen pleomorphism and its relation with allo-antibodies formation(*Please see the Chapter on Transfusion Support in SCD*).
- SCD and Surgery (*Please see the Chapter on SCD and Surgery*).
- **SCD and Pregnancy:** The need for care during pregnancy and postpartum among SCD women is very different from that of normal women. Global studies have shown that if pregnancy occurs in women with SCD, the woman has a risk of maternal and foetal complications, including obstetric complications. However, the 1st prospective study in India among pregnant women with SCD reported successful pregnancy in 84% of cases with zero maternal mortality albeit higher complications of pregnancy, foetus and neonates.[5] Obstetric complications like pre-eclampsia and eclampsia are more in incidence in SCD women than in normal women. Other adverse foetal outcomes like spontaneous abortions and stillbirths are more among SCD mothers. The pregnancy exacerbates the pre-existing anaemia, and there will be increased SCD-related complications like vaso-ocular crisis and acute chest syndrome during the pregnancy. The foetal growth, too, will be affected, and there are chances of preterm deliveries. These reports are based on international studies, and no such data are not available from India, where the haplotype is different from other countries. Hence, more research is required for evidence-based interventions, as women with SCD should be provided with relevant information. They should be aware of complications during pregnancy, possible foetal outcomes, and the importance of antenatal care and prenatal screening. Antenatal care should be very comprehensive. Necessary precautions are to be taken during delivery. (***Please see the Chapter on Management of SCD in Pregnancy***).

• NEWER TREATMENT NEEDS

As mentioned earlier, the pathophysiology, complications and response to therapy vary significantly across the haplotypes. Just to cite a few examples:

1. The iron overload may be variable. Iron overload requiring iron chelation and iron deficiency requiring iron supplementation may be in 10% of cases each.[6]
2. All the Indian prospective trials are unanimous that the low dose of hydroxyurea (10 mg/kg/per day) may be effective in most of the cases. This low dose may have multiple advantages in our set-up.[7,8,9]
3. Many patients are surviving beyond adulthood, getting married and needing pregnancy as well as surgery. Both pregnancy and surgery are high risks.

The concept derived from other studies regarding all the above-mentioned issues may not be true in our patients. Thus we need well-planned research among the institu-

tions to address the above-highlighted issues on a priority basis. (***Please see the Chapters on Assessment of Iron Overload and Chelation Therapy in SCD, Efficacy of Hydroxyurea Therapy in Indian SCD patients, Management of SCD in Pregnancy& Newer Drugs in SCD***).

- **HEALTH CARE**

- **Models of comprehensive SCD care:** The proven interventions for screening, management and prevention are to be integrated rationally. Early detection should be part of this model. Early screening and subsequent care of paediatric patients reduce mortality and morbidity during the early stage of life.

The entire developing countries are looking forward to the Indian model due to geopolitical and scientific reasons. Every planning and health care facility should be equitable as well as accessible. Thus the minimum holistic facilities should be available at the primary health care level. Special facilities like prenatal diagnosis, bone marrow transplantation and others should be available in a few tertiary-level government facilities in the states for easy accessibility and affordability.

- **Provision of care at the primary health care level:** Though efficacious therapies are available, they are not reaching the people and are available in a few urban-based tertiary hospitals. As part of the programme, the primary health care system should be strengthened to screen and manage SCD patients. The primary health care system should be able to guide people for screening or referral and should support the known patients. Simple therapies like hydroxyurea are available and can be used at the primary health care level to manage painful crises among SCD patients.Clear implementation guidelines are needed for the public health system for these activities. A programme should be developed with an appropriate referral system at the primary health care level. The primary health system should be able to implement comprehensive care for SCD with an appropriate referral system. The suggested management guidelines for managing SCD should be popularized amongst the health care providers at the primary health care level, and there is a need to strengthen thereferral system by strengthening the capacity of the health systems. Appropriate training of doctors at primary health centres is identified as a priority. Hence, operational/implementation research has to be undertaken to standardize care in the primary health system.
- **Comprehensive national programme for haemoglobinopathies:** Despite the high burden of SCD and other haemoglobinopathies in India, there are no state-led public health programmes or a health system approach in the country, except for a draft policy notified by the Indian government. Hence, required advocacy is required to initiate the development of a comprehensive national programme by the national government and thereby to implement the programme by the state governments. Research is to be promoted to provide necessary feedback to governments for the development and implementation of the programme.

It is rational to integrate SCD and other haemoglobinopathies like thalassemias in the comprehensive programme, as the approaches of management and prevention and affected populations are the same. Operationally too, it is easier to screen and manage these diseases among the affected populations.

- **Special population needs, equity in care:** As per the current knowledge, the majority of the SCD-affected people are from tribal communities, who are very poor and vulnerable in accessing health care services. They live in remote hilly terrains and forests. Hence, to meet these challenges, the health system in tribal areas is to be strengthened with a focus on improving the facilities' capacity and training doctors and other health care providers. Simultaneously,the community' awareness and felt need are to be generated.
- **Implementation research needs:** To develop and implement the above programmes, implementation research is to be promoted. The population's access to care, improving the quality of care provided by government health centres, and raising awareness among the communities are crucial. Thus the implementation research, aiming at the transition of evidence-based interventions into the programme and practice, can improve the lives

of SCD patients.

• IMPACT OF THE DISEASE

Unlike other congenital blood diseases, SCD carries a massive social stigma and is considered one of the important reasons for the inequity of health care services. Stigma has a tremendous impact on psychological stress, depression, fear, delay in diagnosis, and poorer treatment prognosis, ultimately affecting health behaviours and treatment outcomes. This stigma will be eliminated only when an SCD patient feels that she/he can lead a normal life without any restrictions, marry and with children, and avail accessible and affordable best health care facilities. Advocacy will facilitate in achieving this goal.

Despite the huge burden of SCD in India, no comprehensive data about productivity loss in terms of work or academic performance, stigma and health-related quality of life (QoL) associated with SCD are available. Hence disease impact is not known. Research on stigma and other psycho-social and economic impacts of the disease is to be promoted in the country.

In addition to these data, advocacy campaigns/strategies are to be developed to draw the attention of policy-makers and state-level health care managers. Communities are to be engaged in these efforts, in addition to bringing awareness among them regarding the disease and its management. These efforts are essential in preventing the disease. Research into this concern is almost absent in the country and needs to be promoted.

RECOMMENDATIONS:

1. The unmet medical need and the gap in understanding are huge in India. SCD has a significant socio-economic-health burden. It contributes significantly to IMR, MMR and life expectancy. Its prevalence is so high that it is to be considered a social problem rather than only a medical problem.
2. Besides Sickle Cell Disease, Thalassaemia and HbE Disease are other important haemoglobinopathies in many parts of India. Its impact, management and control involve the same patient pool, samples for investigations, same equipment, same manpower and same logistics, etc. It looks very convincing to integrate SCD, thalassaemia and HbE Disease while planning a programme related to the control or holistic managementof these diseases.
3. Anaemia: the commonest medical problem of India, being prevalent in 64% of the population, contributes to IMR and MMR. Its prevalence has increased by 14% recently despite various control programmes undertaken by the Government of India and all state governments. The anaemia is also related to haemoglobinopathy. Thus it's reasonable to plan one integrated approach to anaemia and all types of haemoglobinopathies.
4. The SOPs based on research from other countries may not be accurate for our patients. It should be designed for our patients based on evidence.
5. National Control and Management Programme should be developed considering all the limitations and feasibility. Advocacy and implementation research are required for this purpose.

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CHAPTER 19

Needs of SCD Community: Patients' Perspective

SRADHITA SAHU, DHENKANAL, ODISHA

At 17 when in the first year of graduation studies, I was in my own zone setting goals for myself and dreaming for a future full of accomplishments. However, my whole world came crashing down around me when I became unconscious following a high fever in hostel.

What was thought to be a simple fever ended up in discovery of a hereditary disease that required a life-long medication and regimented life.

Born to Ramesh Chandra Sahu and Urmilla Sahu in Odisha's Dhenkanal in 1991, I was the 5th amongst the siblings. During the year 1991, when the elder brother encountered some health issues, a doctor was consulted. It was found that he had symptoms of Sickle Cell, and that was inherited heterogeneously from the mother, then rest of the family members underwent checking. I was also diagnosed to have similar disease from my mother.

I had no health issues till 2008 (at the age of 17). The fever that I had in hostel in 2009 led to revelation on my health condition. After the diagnosis, blood level was found to have dropped to 6.8 HB and subsequently I was admitted in ICU for seven days.

At the department of Clinical Hematology of SCB Medical College, I was advised hydroxurea @10mg/kg/day, folic acid, injection methylcobalamin, meningococcal and pneumococcal vaccination with advise for lifestyle modification to prevent VOC.

Though the frequency and severity of pain during crisis has reduced still I was to be admitted intermittently in the SCB MCH and managed. The hydroxurea dose was gradually increased to 20 mg/kg/day and subsequently to 35 mg/kg/day. However, the intermittent pain did not allow me to lead a normal life forcing me to remain away from my office and get hospitalised.

Recently, injection Ryverna was added @250mg IV per dose from August 2022. Meanwhile, I lost my brother to SCD with VOC in August 2022.

I am now 31 year-old and a chartered accountant. Fully financially independent, I want to marry. Few proposals came, but could not be materialised. However, with doctors by my side, I have not lost hope of leading a normal life. I would be lying if I say that I am not facing any stress, strain or mental depression.

SICKLE CELL CRISIS

As per my personal experience, I face the sickle cell crisis when there is

- Sudden change in temperature, basically in winter and summer.
- Dehydration is another trigger.
- Infections.
- Stress.

Here are some ways to help lower one's risk of having a sickle cell crisis:

- Take all medications recommended by your doctor.
- Try to drink about 10 glasses of water a day.
- Try to practice some exercise and yoga to relieve of body pain.
- Avoid stress.

EXPECTATION AS A PATIENT

- The medical professionals should find a solution for SCD so that we can lead a painless normal life and start own families with children after marriage.
- Government should do all the needful and provide special care to SCD community.

ASHISH PRADHAN, ANGUL, ODISHA

Sickle Cell Disease (SCD) is a genetic disorder that affects millions of people in the global. Unfortunately, I am one among the millions affected by SCD (homozygous), which I was diagnosed at the age of one.

Till 17 years of age, I had gone through severe pain crisis with blood count plummeting 2 to 3 times in a year. I turned to painkillers to manage pain and antibiotics to check fever. Around 11 to 12 units of blood were required to be transfused at the time of low hemoglobin.

Hydroxyurea was not prescribed to me. Subsequently, I approached Hematology department of SCB MCH, Cuttack, where I was administered hydroxurea and folic acid. I have now completed my graduation and studies.

With the same medications till now there is no severe crisis. Four to five episodes of mild pain have definitely occurred. Recently, I was vaccinated with meningococcal and pneumococcal vaccines.

I sincerely thank all my doctors for showing their great humanity and dedication in their treatment and their kind behaviour towards me during every phase of my life.

So, suffering with the disease I would like to share some of my experience:

• HOW SCD AFFECTS YOU IN DAY-TO-DAY LIFE?

Growing up as a child it affects you in every stage of your life starting from studies, sports, playing games to colleges and even sometimes you just have to compromise with your career. It affects in doing normal job or business. Family members come under pressure to manage the crisis.

• HOW IS IT TREATED AND MANAGED?

In earlier days, it was quite difficult to live with SCD. One had to frequently go through the crisis and poor quality of life. Nowadays, one can access advanced treatment with usage of Hydroxyurea that limits the pain crisis and blood transfusion. It also helps prevent organ damage.

With regular medications including folic acid, multivitamins and calcium one gets a productive life. Whenever one faces a crisis, he or she has to have proper medication, intake of sufficient fluids and care.

• HOW DIET AND LIFESTYLE HELP YOU?

One has to be very careful towards one's body. One needs to take proper balanced diet, good amount of water, moderate yoga and exercise along with regular medication. In my experience, healthy lifestyle, adequate hydration and a complete stress free life have benefited me. As much you take care your body, it would definitely support you in the future. Always avoid oily and fast foods, dehydration, extreme climate, hard work and stressed mind.

EXPECTATION AS A PATIENT

- In our country we have poor healthcare facilities and infrastructures and lesser number of doctors. We need a good healthcare eco-system to support the patients in the time of emergency and crisis.
- Along with this we always need a great support from the doctors not only for treatment as well as from psychological and educational point of view.
- We need to spread proper education and awareness about the disease among the patients and family members as to how the SCD could be effectively managed throughout the life.

CHAPTER 20

Roadmap for SCD in India

The Sickle Cell community in India is the fiercest of warriors in the literal sense. They not only battle the harshest of physical suffering but also gross social misconceptions, including stigma, health care inequities and general lack of awareness. We need to have a roadmap to bring them to the mainstream by ensuring everyone has access to comprehensive care. We need an action plan, and work on mission mode towards prevention and control of SCD. We need to ensure - No One Is left Out

~Prof RK Jena

Recognising SCD as a major public health issue and concern at the national and state-level is the first step towards combating the disease in the country. Despite having a prevalence of nearly 5% of India's population, which in sheer numbers translates to more than 6 crore affected people, Sickle Cell Disease (SCD) continues to be neglected as a public health issue. Lack of proper recognition and importance to the disease in major health policies and health systems has not only deprived the SCD community in the country from comprehensive care but also led to marginalisation in many aspects. Along with the excruciating suffering from the affliction, the patients also have to battle social stigma.

While there is inequity in health care system, medical advances that can bring more relief to the SCD patients have not been made accessible to them. Thus, a major chunk of the patients continue to live with serious unmet medical needs.

Besides, there has been no concerted research on the genetics and unique features of SCD gene in Indian context. Whatever existing data is derived from other haplotypes like Senegal and Bantu, while there is paucity of data related to Arab-Indian haplotype which is dominant in our country.

Patient profile or the phenotypes, complications and results hugely vary across the haplotypes. Medical needs including risk prediction, effectiveness of infection prophylaxis, iron overload and chelation, cardio-pulmonary and neurological complications, management of pregnancy and surgery with SCD and transfusion-related complications need to be studied in the haplotype found in India.

Huge infrastructure deficiencies lack of pre-natal diagnosis (PND), bone marrow transplant, extended cross-matching, availability of drugs, monitoring, nutritional deficiency and an amicable control environment are major drawbacks. Sub-optimal utilisation of existing healthcare facilities due to various challenges is also a concern.

The SCD community residing in tribal areas and villages is worst affected and deprived of the minimum facilities and very much rejected with feeling of being neglected and marginalised by the government. There is a huge dissatisfaction and anger within the community without any systematic expression or demand because of existing social stigma.

Thus, a strategic plan with roadmap for holistic implementation of SCD community in the country is the need of the hour.

OBJECTIVE

The first and foremost goal is to ensure every person with SCD in every corner of the country is identified and provided with appropriate health care in time. The goal should be to put systems in place to identify and reach out to every person with SCD with necessary health care and social support services.

For achieving this, there needs to be a sustained effort involving the central and state governments, ISHBT (ICH), ICMR and other health care professionals' bodies, NGOs and social organisations, patient organisations and all other stakeholders concerned.

Screening and identification initiatives should be strengthened. Healthcare infrastructure should be ramped

up across the country, particularly in the high incidence regions, with trained manpower and adequate support systems to reach out to the persons with SCD and provide timely interventions.

SCD population should receive high quality healthcare in comparison to their normal counterparts. This would assure 'long, healthy and productive lives' for those living with SCD.

A strategic plan and a defined roadmap are required to make this possible. The plan should be based on the seven fundamental pillars – **Identification, Accessibility, Efficient, Quality, Safe, Equitable and Empowering.**

STRATEGY -1: IDENTIFICATION (TIME FRAME 3-5 YEARS)

For any major public health issue, the first and foremost challenge is to accurately determine prevalence, burden and spread from the region down to the community-level. Disease registry is imperative for any prevention and control programme. It provides a baseline for assessing the magnitude of problem at hand and for planning the necessary services.

Therefore, SCD registries should be initiated in a comprehensive manner both at the hospital and population-level.

(a) **Hospital-based registry –** The hospital-based registry will include all patients diagnosed or treated by a particular institution for SCD, whether in-patient or out-patients. The registry should collect the uniform set of data along with possible linkage to treatment and follow up. The hospital-based registry can be of considerable value in the evaluation of diagnostic and treatment programme. Since hospital population will always be a selected population , the use of these registries for epidemiological purposes will be limited.

(b) **Population-based registry –** The population-based registry will cover the prevalence as well of phenotype of SCD as well as trait in a given geographic area. The data from such registries alone can provide the incidence rate of SCD and serve as a useful tool for initiating epidemiological inquiries into surveillance of time trends and planning and evaluation of operational activities in areas of SCD prevention and control.

RECOMMENDATION:

1. Establish a national data-system or registry in convergence with all State-level hospital-based and population-based registries to collect and collate data in a uniform database. This will help in studying the epidemiology and burden and also evaluating the outcomes of interventions on the ground. It will guide formulation and implementation of an effective national plan for prevention and control of SCD in India.
2. The national registry may be integrated with beta-thalassemia, HbE and other Haemoglobinopathies.
3. The apex body should be at Delhi – Health Ministry/MOTA/NHM.
4. All states should have their zonal headquarters at respective NHMs.
5. Each state should have a CoE – 2-4 in numbers to coordinate and monitor all aspects including screening, provisioning of health care and outcomes.
6. It will help augment existing health care system and trained personnel along with infrastructure as per the decision of the state concerned.

STRATEGY -2: ACCESSIBILITY (TIME FRAME 3-5 YEARS)

Provisioning of holistic health care facilities both clinical and non-clinical to all persons living with SCD is the key to combating the public health challenge. There should be an organised model of providing clinical and non-clinical services and supportive interventions for SCD. SCD health care should be integrated from the primary care-level up to the tertiary and CoE structure. Efforts should be made to make high quality, comprehensive and speciality care with a multi-disciplinary approach accessible to each and every person with SCD in the country.

RECOMMENDATION:

1. Comprehensive care centres with necessary infrastructure, human resources and facilities should

be made available across the country which should be affordable as well as accessible.
2. A national SOP regarding the diagnosis, monitoring and management should be designed after consultation with ISHBT and ICMR and other stakeholders.
3. Laboratory infrastructure should be improved at the primary health care-level for early detection of SCD.
4. Referral facilities should be strengthened at DHH-level to manage SCD.
5. A module for training of doctors and health care givers and ICE matter for patients and public should be designed.
6. Vocational rehabilitation programme should be integrated with health care.
7. Disability facilities should be strengthened.
8. Education department should be involved to provide a modified version of education system for mainstreaming SCD patients.
9. Social, Tribal and other departments concerned should be involved both at national and state-level.

STRATEGY – 3: EFFICIENT (TIME FRAME 2-4 YRS)

Trained health care personnel and allied human resources from the top to the grassroots are imperative for any effort towards effective control and management of SCD in India. Apart from increasing the number of doctors in speciality care, there is an urgent need to enhance SCD management capabilities among personnel posted at the primary care-level as well as general physicians in the community. Trained doctors, allied personnel will ensure early detection, efficient primary care, timely referral as well as life-saving interventions which will not only reduce mortality and morbidity among SCD patients but also vastly improve overall health outcomes.

RECOMMENDATION:

1. A training module for SCD care should be created by ISHBT, ICMR and other stakeholders.
2. Comprehensive training should be given to all doctors posted at PHCs, CHCs, SDHs, DHHs, etc, which are the primary point of care for all SCD patients.
3. Laboratory personnel at the grassroots level should be trained for SCD.
4. Nursing personnel should also be given training on specialised care for SCD.
5. All involved caregivers should receive periodic training with skill-upgradation to keep up with advances and changes in SCD care.

STRATEGY 4: QUALITY (TIME FRAME 2-3 YEARS)

Quality and efficiency of SCD care can only be achieved through constant monitoring at every level. There should be efforts to strengthen and integrate evidence-based interventions for enhancing quality of SCD care.

RECOMMENDATION:

1. A third party should be involved in conducting research to assess the quality of the available health care, its gaps and solutions thereof.
2. ICMR, other independent organisations can be involved for such activities.
3. The recommendations should be studied and acted upon in a timely manner so that improvements can be made for the benefit of the patients as well as enhancing strategy planning.
4. A multi-disciplinary approach should also be adopted for further development of clinical practice guidelines and enhancing quality of care.

STRATEGY 5: SAFE (TIME FRAME 2-4 YEARS)

Establishment of CoE with research activity and allocation of funds for the purpose. There should be at least, two CoEs in each state.

RECOMMENDATION:

1. CoE will function as referral centre for overall man-

agement of complicated/undiagnosed SCD cases.
2. Will issue direction as per the need to all the downstream centres.
3. Extensive research activities related to various aspects of SCD should be taken up among Indian patients so as to validate the concept derived in other countries or create a new concept which will be beneficial for the management of Indian patients.
4. They will be responsible for training of health care professionals, allied personnel.
5. They can modify the SOPs depending on the advances and changes in care systems.
6. Ensure establishment of new technology and services in centres as per the need.
7. They will provide technical advice to govt and other related agencies

STRATEGY 6: EQUITABLE (TIME FRAME 3-5 YEARS)

Awareness and advocacy are key components for success of any prevention, control and management programme. SCD care in India should integrate holistic awareness generation programme along with strengthening advocacy which will not only educate the persons with the disease but also sensitise the society on this crucial public health issue. It will give a boost to SCD support systems while making the community at large more sensitive, compassionate and alive to the problem. Through awareness and advocacy, prevention and control efforts will gain strength. It will also help policy and strategy panning for SCD in the country.

RECOMMENDATION:

1. Governments, health care providers, social organisations, all stakeholders and media should be involved in creating awareness about SCD.
2. Special campaigns should be launched to sensitise the general communities on SCD regarding the availability and utilisation of holistic health care facilities and break the social taboos and end discrimination of the sufferers.
3. ICE modules at the national-level as well as region-specific ones (considering the unique situation in a particular state or region) should be developed and disseminated among all stakeholders.
4. Collaborative efforts among advocacy groups, NGOs, community leaders, teachers and students, etc., should be strengthened for generating awareness.

STRATEGY 7: EMPOWERING (TIME FRAME 2-3 YEARS)

Breaking the barriers which prevent accessing therapies for SCD is a major aspect of universalising SCD care. Besides, persons with SCD should be empowered with all support systems to lead a normal life with dignity and freedom. All social stigma and taboos attached with SCD should be eradicated through sustained efforts to address the myths and misconceptions around the disease.

RECOMMENDATION:

1. Mission mode campaigns to eradicate the social stigma around SCD.
2. Education, vocational, rehabilitation, skill-development initiatives to be strengthened for empowering persons with SCD to lead a dignified life.
3. A clear guideline to be created for overall management of SCD. This should be simple, realistic and workable.
4. Procurement, availability and distribution of drugs should be adequate across the place and time.
5. Efforts should be made for procurement of new and effective drugs.
6. Facilities of PND, bone marrow transplant and other health care should be available in efficient way.

NATIONAL GUIDELINES ON MANAGEMENT AND CONTROL OF SICKLE CELL DISEASE

INDIAN COLLEGE OF HEMATOLOGY (ICH)

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INDIAN COUNCIL OF MEDICAL RESEARCH (ICMR)

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NATIONAL GUIDELINES ON CONTROL AND MANAGEMENT OF SICKLE CELL DISEASE