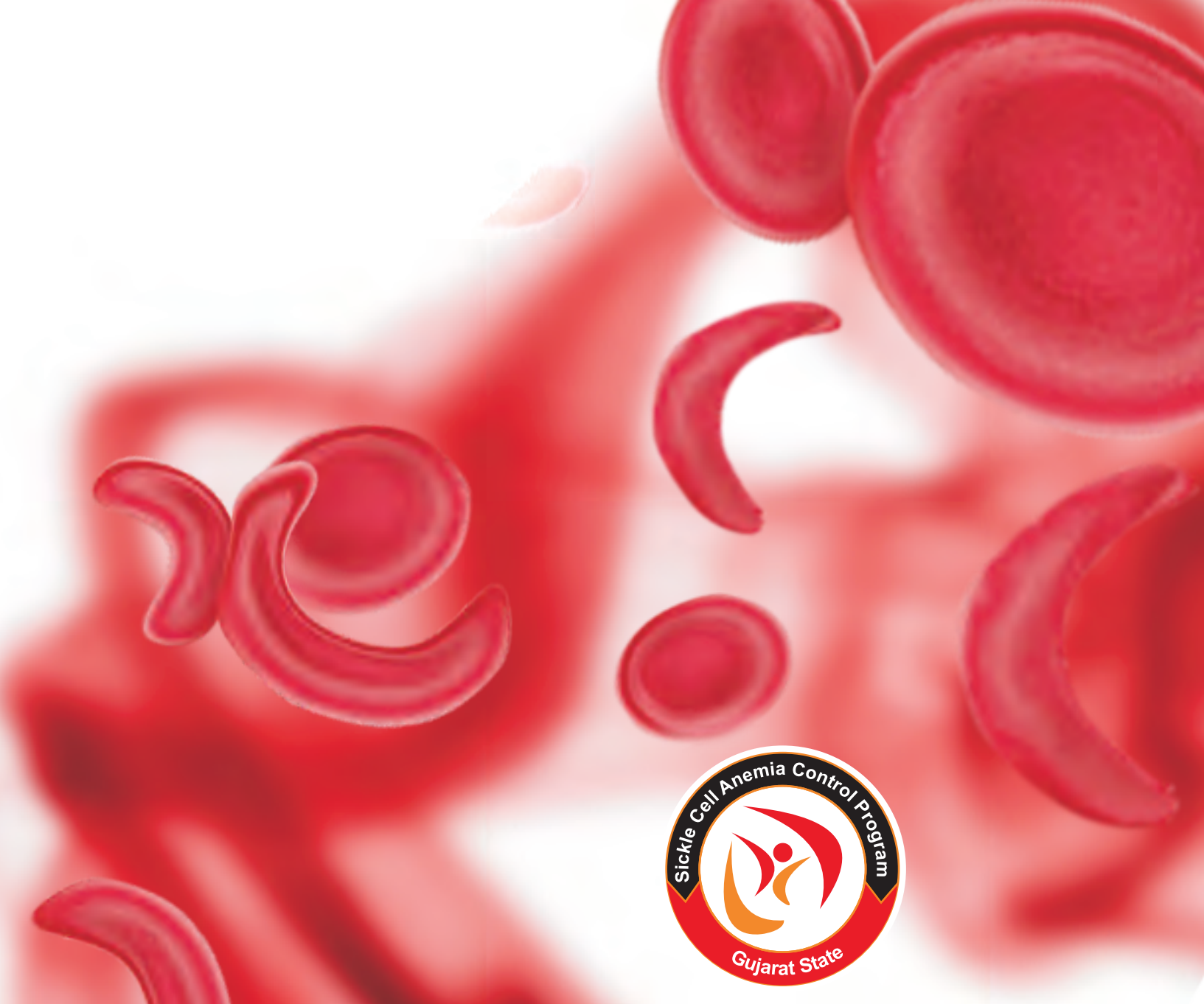

Sickle Cell Anemia

Program Manual

Epidemic Branch
Commissionerate of Health
Family Welfare and Medical Services
Gandhinagar, Gujarat.

Sickle Cell Anemia Control Program Manual

(In accordance with Department of Medicine, GMC, Surat)

Epidemic Branch
Commissionerate of Health, Family Welfare and Medical Services
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Contents

Introduction

Sickle Cell Anemia (SCA) is a hereditary anemia predominantly seen amongst various tribal populations of India. Sickle Cell Anemia occurs due to inherited abnormal haemoglobin (Hb) gene, which produce Hb-S (Hb-Sickle). This disease has not gained much concern at national as well as state level. Screening is not a common practice and the diagnosis is usually made when a patient presents with severe complications. Patients affected by SCA are frequently misdiagnosed and mistreated as most common iron deficiency (nutritional) anemia with iron therapy.

Normal human Red Blood Cells (RBCs) carries Hb-A (adult haemoglobin), which helps RBCs in transportation of oxygen in the body. In case of Sickle Cell RBCs, on de-oxygenation (after transferring oxygen to body tissues) because of the presence of Hb-S and because of its abnormal characteristic, converts RBCs into rigid-brittle half moon (Sickle) shaped instead of soft round biconcave shape.

Life span of RBCs in Sickle Cell Disease (SCD) is less than 30 days instead of 90 to 120 days. Anemia results from the bone marrow's inability to produce enough blood cells to keep pace with the rate of destruction.

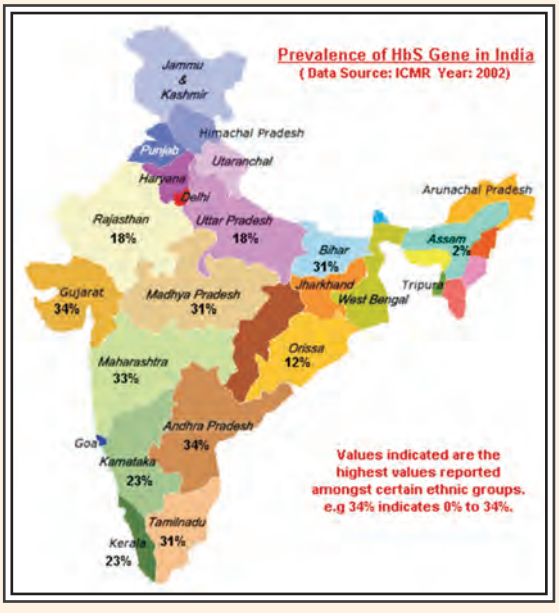
Sickle gene is found all over the world, particularly amongst people originated/migrated from Malaria endemic areas of Africa & Asia. According to one of the hypothesis, it is a natural mutation in haemoglobin molecule to protect RBCs from malarial parasites by making them a little rigid, so that malarial parasites can not enter into RBCs. This is the reason why Sickle Cell gene is present amongst tribal group mainly, who originated from malaria endemic forest areas.

Since the development of Microscope by Jansson in 1950, Sickle cell is the first red cell abnormality that was found out in 1910 by James Herric. And since then lots of research has been done in the field of Sickle Cell Anemia all over the world but very little work was done particularly in India. In 1952 Lehmann & Cutbush reported Hb-S in tribal population of Nilgiri in South India. And after that many research papers have been published in the scientific journals but the fruits of the research had not reached to the common disease suffering tribal people. All these publications were carried out as a part of Ph.D. thesis or M.D. dissertations. Many research on SCA/SCD remained restricted to publications. The results of research were not shared with medical fraternity especially those doctors who were practicing in tribal areas of India, making them unaware of the existence of Sickle gene in tribal population. This had resulted in misdiagnosis and mistreatment.

Early diagnosis and institution of treatment is critical in SCD because of the possibility of lethal complications in early infancy in pre-symptomatic children. Children with SCD have an increased susceptibility to bacteremia due to Streptococcus pneumoniae which can occur as early as 4 months of age and carries a case fatality rate as high as 30 percent. Acute splenic sequestration crisis, also contributes to mortality in infancy.

Prevalence of Sickle Cell Anemia

Hemoglobinopathies including Thalassemia with an estimated 10,000 live births each year and Sickle cell Disease (SCD) with an estimated 5,200 live births each year are a major public health problem in India.



Although SCD has been described in India in numerous ethnic groups, it is most prevalent among indigenous ethnic groups, classified as scheduled tribes, who have a high prevalence of socio-economic disadvantage and are frequently medically underserved.

ICMR took initiative in the year 1987 and again in 1999, to quantify the burden of Sickle Cell Gene in India through its multi centric project and has published following results.

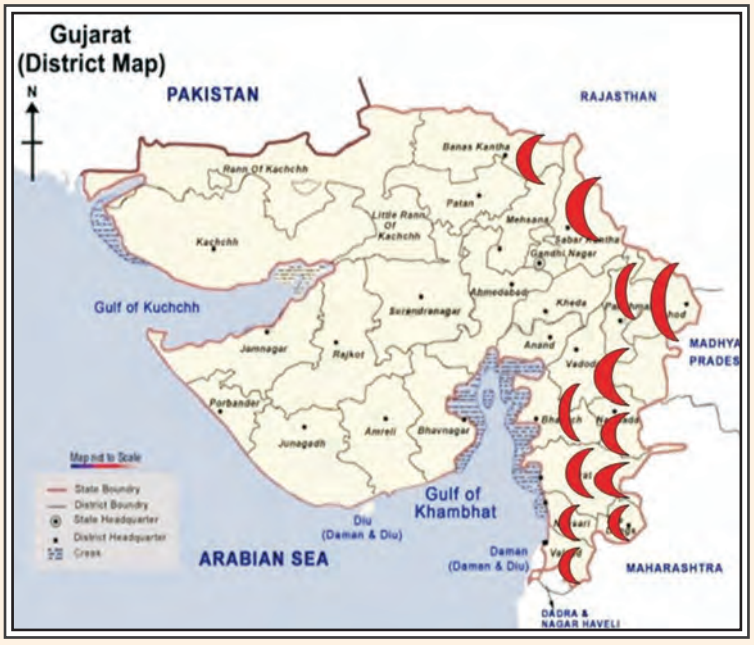
According to ICMR survey Sickle Cell gene is found amongst different tribal groups of India, which varies from 5 to 34 %. According to WHO, 10 % of Sickle Cell Disease patients die by the age of 1 year and in many sub-Saharan countries mortality is much higher than that.

India has also a very huge population of tribal community about 18 crore and expected to have 1.80 crore Sickle Cell Trait and 14 lakhs of Sickle Cell Disease. This shows the big burden on the public health of India.

Estimated Prevalence of Sickle Cell Anemia in Gujarat and India (Year 2011)

	Gujarat	India
Total Population	6,03,83,628	1,21,01,93,422
Tribal Districts	12	593
Tribal Population @ 14.76%	89,12,623	17,86,24,549
Estimated Person with Sickle Trait @ 10.0 %	8,91,262	1,78,62,455
Estimated Person with Sickle Cell Disease Patients @ 0.75 %	66,845	13,39,684

Other states like Maharastra, Chhattisgarh, Madhya Pradesh, Orissa, Andhra Pradesh and Tamil Nadu also has a problem of Sickle Cell Anemia in Tribal area in variable quantum.



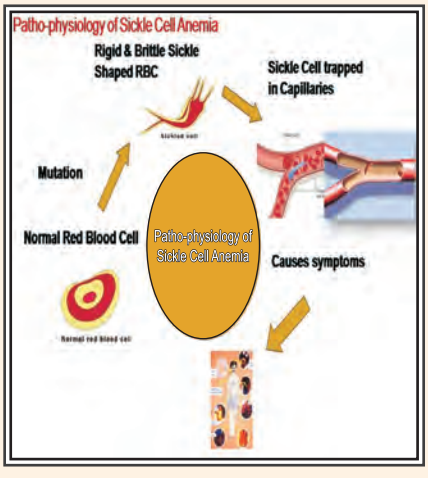
Gujarat has 89.12 lakh tribal population and is expected to have at least 9,00,000 Sickle trait and 70,000 Sickle Cell Disease patients. The Dhodia, Dubla, Kukna, Gavit, Chaudhary, Halpati, Varli, Kokni, Kathodi, Kolcha, Kotwadia etc. are among the major tribes having Sickle Cell problem in Gujarat. According to ICMR survey amongst the primitive tribes of south of Gujarat, viz; Kolcha, Kotwadia & Kathodi; 30 % of Sickle Cell Diseased children die before they reach adulthood (14 years) and the remaining 70 % die by the age of 50.[4]

Pathophysiology & Clinical Manifestations of Sickle Cell Anemia

Normal human Red Blood Cells (RBCs) carries Hb-A (adult haemoglobin), which helps RBCs in transportation of oxygen in the body. In case of Sickle Cell RBCs, on de-oxygenation (after transferring oxygen to body tissues) because of the presence of Hb-S and because of its abnormal characteristic, converts RBCs into rigid-brittle half moon (Sickle) shaped instead of soft round biconcave shape.

The rigidity and abnormal shape reduce RBC's ability to be propelled through tiny capillaries & thus there is formation of entangled masses of red blood cells in larger blood vessels. This obstructs the blood flow into organs, producing temporary or permanent organ dysfunction or structural changes and retarded growth. Because of their abnormal shape, the spleen in the body destroys these RBCs, causing enlargement of spleen. Life span of RBCs in Sickle Cell Disease (SCD) is less than 30 days instead of 90 to 120 days. Anemia results from the bone marrow's inability to produce enough blood cells to keep pace with the rate of destruction.

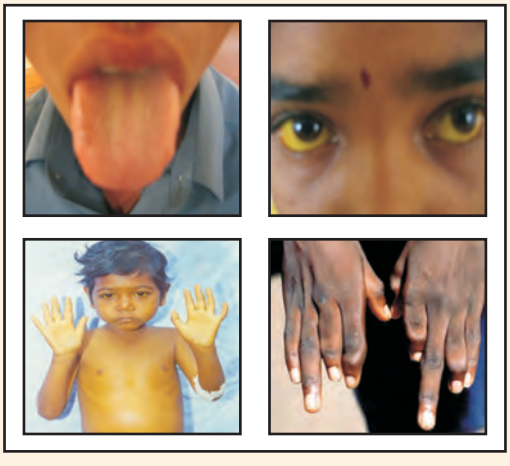
- Inflexible Sickled red blood cells trapped in narrow vessels
- Blood Flow Slows Down
- More RBCs become deoxygenated and Sickled and
- Capillaries are blocked.



The obstruction of the blood flow produces temporary or Ppermanent organ dysfunction or structural changes (damage to the organs), leading to multi organ damage all over the body. This has created other health issues, increasing morbidity and mortality

Symptoms of Sickle Cell Anemia:

- Pallor
- Frequent jaundice
- Bone ache & Body ache
- Enlarged Spleen
- Retarded Growth
- Frequent Infections
- Dactylitis (Hand-Foot Syndrome)

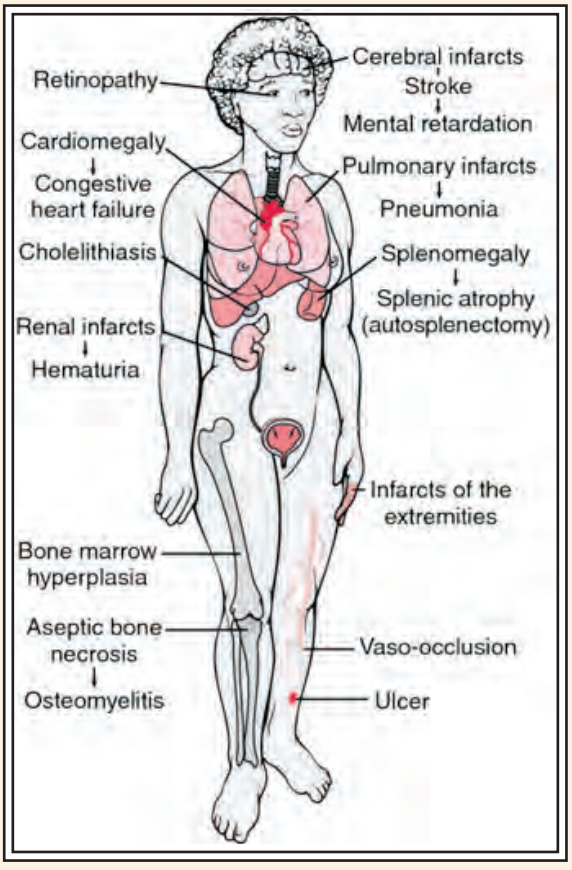


Major Clinical Menifestations

1. Anemia
2. Sicle Cell Crisis
    a. Acute Painful Episodes
    b. Abdominal Pain Crisis
    c. Splenic Sequestration Crisis

d. Aplastic Crisis
e. Hemolytic Crisis

3. Psychosocial Issues
    a. Cultural, educational and employment issues
4. Infections
    a. Bacteremia
    b. Meningitis
    c. Bacterial Pneumonia
    d. Osteomyelitis
5. Musculo-Skeletal Complications
    a. Dactylitis
    b. Avascular Necrosis of Bone
    c. Growth And Development Delay
    d. Osteomylitis
    e. Arthritis (septic-reactive)
6. Dermatological Complication Leg Ulcer
7. Priapism
8. Cerebrovascular Events
    a. Cerebral infarction
    b. Intracranial hemorrhage
    c. Cognitive and behavioral changes
9. Cardiac Complications
    a. Myocardial Infarction
    b. Cardiomyopathy
10. Hepato Billiary Complications
    a. Cholelithiasis
    b. Hepatic sequestration crisis
11. Pulmonary Complications
    a. Acute Chest Syndrome
    b. Pulmonary Hypertension
12. Renal Complications
    a. Papillary Necrosis, Acute and Chronic Renal Failure.
13. Occular Complications
    a. Proliferative Sickle Retinopathy
14. Pregnancy related complications
    a. Leading to increased maternal and fetal morbidity and mortality
15. Multiorgan Failure



Diagnosis of Sickle Cell Anemia

Diagnosis of Sickle Cell gene can be done by easy sickling test, which can be performed in the field also. The confirmation whether the person is Sickle Cell Trait or Sickle Cell Disease, two tests can be done.

1) Electrophoresis
2) HPLC

DTT (Di-ethionide Tube Turbidity Test)-

Principle:
Sickle Cell hemoglobin is insoluble in the deoxygenated state in a high molarity phosphate buffer. The crystals that form refract light and cause the solution to be turbid.

Reagents:
Phosphate buffer (P_H7)
Sodium dithionate powder
Normal Saline

Preparation of Phosphate Buffer:

K_2HPO_4	:	250	gm
KH_2PO_4	:	143.5	gm
Saponin	:	2	gm
Benzoic Acid	:	2.5	gm
Distilled Water	:	1	ltr

Note: This reagent buffer is stable for 6-7 days at room temperature and for 1 Month at 4°C. Sodium dithionate powder should be kept in air tight container at room temperature.

Required Blood Collection: 2ml in EDTA bulb

Preparation of Packed cell:
1 Fill the small test tube (12 X 75 mm) with approximately 2 to 3 ml Normal saline.
2 Add 2 to 4 drops of well mixed whole blood from EDTA tube.
3 Mix thoroughly and centrifuge it at 3000 rpm for 2 minutes.
4 Discard the supernatant and add 2 to 3 ml Normal saline again for cell washing.
5 Repeat cell washing three times and after 3rd washing discard supernatant.

Method:
1 Take a pinch of sodium dithionate powder in test tube (100 X 12 mm).
2 Add approximately 1ml of phosphate buffer and mix well till Sodium Dithionate powder is dissolved.
3 Add approximately 10 to 20 micro liter of three times washed red blood cell and shake gently.
4 Allow it to stand for 5 minutes.

Interpretation of solubility / DTT Test Results:

Positive **Negative**

1 The color will be pinkish violet.
2 Look for turbidity against two dark black lines on white paper against a bright source of light.
3 Keep tubes 1cm away from paper.
4 If turbidity seen -Solubility test is positive -dark black lines do not appear clearly through tubes.
5 If Turbidity not seen -Solubility test is negative -dark black lines appear clearly through tubes.
6 If tubes are allowed to stand for more than half an hour, a ring formed by insoluble Hb S is seen on the surface of the test reagent.
7 Known Positive Control and Negative Control should be kept to compare the result.

Management of Sickle Cell Crisis

- **Painful Crisis**
  - **Clinical Features**
    - Persists for 4-5 days sometime longer
    - Acute onset gnawing progressive deep-seated pain
    - Described by the patient as "typical sickle cell pain"
    - Pain can vary from Mild (barely interfering with normal lifestyle) to Excruciating ("worse than breaking a leg)
    - Arthritis/arthralgia like presentation
    - Mild erythematic and warmth
    - Local tenderness-usually present
    - Difficult to differentiate from osteomyelitis, rheumatic fever… osteomyelitis is likely if fever >39.4 degree Celsius.
    - Fever-usually mild
    - Leucocytosis may be there
  - **Precipitating Factors**
    - Infection
    - Fever
    - Dehydration
    - Acidosis
    - Cold
    - Emotional stress
    - Physical exertion
    - Menses and pregnancy
    - Alcohol consumption
    - Sedatives and local anaesthetics
  - **Management**
    - Identify precipitating cause and treat it
    - Fluid Management
    - Normal Maintenance requirement in children is based on body weight
    - 1-10 kg (100 ml per kg)
    - 1-20 kg (for first 10 kg, 100 ml per kg = 100x10 = 1000 ml. For remaining kg, 50 ml per kg. for example 18 kg childs normal maintenance requirement 1000 ml plus 50x8 = 400 ml total 1400 ml. sickle cell child with 18 kg weight will require 1.5 x 1400 = 2100 ml fluid in 24 hours.
    - 1-40 kg (1500 ml for first 20 kg + 20 ml per kg for remaining kg)
    - For children use isolyte -P, for adolescent use DNS
    - Maintain electrolyte balance
    - Correct Acidosis Sodium Bicarbonate (without arterial blood gas analysis maximum 1ml per kg I.V.)
    - Treat infection – Antibiotics

- Oxygen if hypoxia (SPO_2 less than 92% with pulse oximeter with nasal canula 2 liters per minute and for nasal mask 5 liters per minute and for hood 8 liters per minute)
- **Analgesics**
  - Fortwin (Pentazocin) Commonly used drug, may be used s.c/i.m/ i.v. with the dose of 30-60 mg qid in adults and 1 ml/kg in children 1 mg/kg. Avoid intramuscular, if poor venous access give subcutaneous. Avoid combining pentazocine with codeine or morphine.
  - Dose of i.v. morphine is 0.1-0.15 mg/kg loading followed by maintenance dose 0.05-0.10 mg/kg can be given every 6 hourly keeping watch for respiratory depression. Oral dose 10-30 mg every 3-4 hourly.
  - Paracetamol iv infusion\i.m.\oral 500 mg tid (upto 4 gm/day), In children 15mg/kg orally can be repeated every 6 hourly.
  - Diclofenac 50 mg tid, upto 150 mg/day in 2-3 divided doses. In children, 1-3 mg/kg sos orally can be repeated every 8-12 hourly.
  - Ibuprofen 300-400 mg qid (upto 2.4 gm/day), in children 10-15 mg/kg orally 8 hourly.
  - Tramadol : 50-100 mg bid/tid. (upto 400mg/day) oral/i.m./i.v./s.c. preparation available. It is safely used in renal impairement patients upto 200 mg/day, and hepatic impairement upto 100 mg/day.
  - Ketorolac : Parenteral/Oral 30-60 mg- adults;1-1.5 mg/kg – children - not to exceed 5 days
  - Codeine : 30 mg 4-6 hourly (upto 240mg/day)
  - Naproxen : 250-500 mg bid, upto 1250 mg/day
  - Indomethacin : 50-200 mg/day in devided doses with food.
  - Aspirin is avoided in children due to a risk of Reye's syndrome.
  - All NSAIDs should be taken with food. Avoid NSAIDs in patients with Hepatic failure, peptic ulcers, coagulopathies, severe dehydration and renal failure. Chronic use should be avoided to prevent renal damage.
  - One or more drug can be used in combination according to severity of pain. In case of severe pain crisis, opioids drugs like morphine can be used.
  - Folate supplements, 1mg orally daily in children

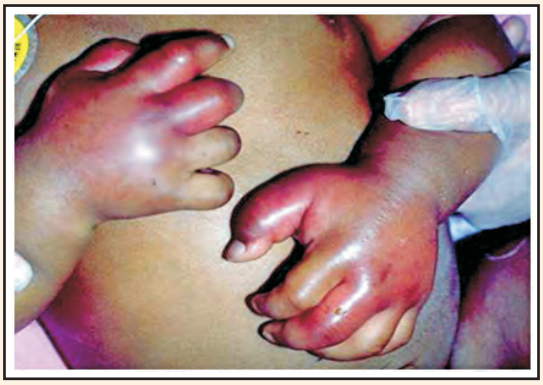
- **HOME TREATMENT**

  - **All patients with SCD should be educated** to start with
    - Heating pads
    - Oral fluids
    - Acetaminophen/ibuprofen
    - If appropriate home management fails
    - If not relieved of symptoms, approach hospital.

- **Dactylitis- Hand Foot Syndrome**

  - **Clinical Features**
    - Occurrence of painful VOC in the small bones of hands and feet
    - Occurs in infants

- Painful, often asymmetrical swelling of hands and feet
- Mild erythema
- Low grade fever
- Soft tissue swelling
- Recurrent episodes – lead to a mottled appearance of small bones of hands or feet on x-ray.



- **Treatment**
  - Maintain Hydration
  - Analgesic and anti-inflammatory medication and
  - Hot packs

- **Avascular Necrosis (Osteonecrosis)**
  - Bone and joint ischemia can lead to aseptic necrosis, especially of the femoral or humeral heads; chronic arthropathy; and unusual susceptibility to osteomyelitis, which may be caused by organisms, such as Salmonella, rarely encountered in other settings.
  - **Clinical Features**
    - Presents with insidious onset of Pain in hip.
    - Brought on walking or doing quick activities.
    - Localized to groin or buttock.
    - Diagnosis by X-rays or MRI
  - **Treatment**
    - **A. Conservative Measures.**
      - Bed rest
      - Non weight bearing with crutches.
    - **B. Total hip replacement.**
      - Done in cases of painful hip in stage 3 or 4 or for restoration of joint movement.

- **Abdominal pain crisis**
  - Abdominal pain can be severe, resembling acute abdomen; it may result from referred pain from other sites or intra-abdominal solid organ, mesentery or soft tissue infarction. Reactive ileus leads to intestinal distention and pain.
  - **Clinical features:**
    - Severe abdominal pain.
    - The pain may or may not be localized to any one area of the abdomen.
    - Signs of peritoneal irritation.
    - Bowel sounds present.
    - Nausea, vomiting, and diarrhea may or may not occur.
  - **Treatment**
    - Prompt intervention
    - Hydration(100-150% of normal daily fluid needs)
    - Warm packs to the affected area.

- Analgesic and anti-inflammatory drugs.
- Needs to be differentiated from acute abdomen- needing surgical intervention

- **Acute chest syndrome**

  Acute chest syndrome is thought to reflect in situ sickling within the lung, producing pain and temporary pulmonary dysfunction. It is characterized by chest pain, tachypnea, fever, cough, and arterial oxygen desaturation. It should be differentiated from pneumonia, pulmonary emboli, bone marrow infarction and embolism, myocardial ischemia, or in situ lung infarction. Acutely, reduction in arterial oxygen saturation is especially ominous because it promotes sickling on a massive scale. Frequent episodes of acute chest pain correlate with reduced survival. Chronic (long-term) sickle cell lung disease like Pulmonary hypertension and Cor-Pulmonale develops with time.

  - **Precipitating Factors**
    - Infection
    - Vaso-occlusive
    - Post operative complication
    - Asthma
    - Chronic hypoxia

  - **Diagnosis- Clinical and requires BOTH of the following criteria**
    1. A new pulmonary infiltrate detected on chest X-Ray involving at least one complete lung segment
    2. AND one more of the following
       - Chest pain
       - fever > 38.5ºC
       - Any one of following respiratory findings (Tachypnoea, wheezing, cough or appearance of increased work of breathing.)
       - Hypoxemia relative to baseline measurement.

  - **Management ACS**
    - Acute chest syndrome is a medical emergency and must be treated immediately.
    - Managing severe ACS is challenging.
    - Support in an ICU is usually necessary
    - The goal of therapy - to correct the underlying causes that cause deoxgenation of Hb S that lead to Sickling of RBC and ischemia and injury to lung tissue.
    - **Intravenous fluids:** Hypovolemia can cause increased Sickling. Close monitoring watch for pulmonary oedema. Normal I.V. maintenance, if suspecting pulmonary oedema give frusemide.
    - **Analgesia:** Control of abdominal, thoracic and spinal pain is important to prevent hypoventilation. (Avoid over sedation by opoids.)
    - **Transfusion therapy:** Improves oxygenation.
    - **Respiratory Support:**
      - O_2 supplementation- maintain oxygen saturation $\geqslant$ 92%
      - Poor respiratory efforts or rising O_2 requirements- positive pressure ventilation.
      - Mechanical ventilation for respiratory failure.

- **Antibiotics:**
  - Infection: 3rd gen cephalosporin (ceftriaxone 2-4 gm/day in 2 divided doses) PLUS add a Macrolide- Azithromycin- 10 mg / kg / day single dose / Erythromycin 30 mg / kg / day 3 divided doses for atypical organisms.
  - Add Inj. Vancomycin 10-15mg/kg i.v. 8 houry for severly ill febrile patients.
  - Inj. Clindamycin 10mg/kg i.v. 6 hourly for patients having known or suspected Cephalosporin allergy.
  - Other antibiotics can be added according severity, type of infection and Culture-Sensitivity report.
- **Blood Transfusion:**
  - Improves oxygenation of SCD patients.
  - Considered early in the course of the disease.

- **Infections:**
  It occurs typically in tissues those are susceptible to vaso-occlusive infarct (Bone, Kidney and lung.) Staphylococcus spp., Salmonella spp. and enteric organisms are most common. Pneumonia is most likely to be caused by Mycoplasma pneumoniae, Staphylococcus Aureaus and H. Influenzae must be distinguished from Acute chest syndrome.

- **Leg Ulcers:**
  It occurs at the ankle and is often chronic and recurring.

- **Pregnancy:**
  In a patient with sickle cell anemia, Pregnancy should be considered high risk and is associated with increased spontaneous abortion or premature delivery, along with increased vaso-occlusive crisis.

- **Liver diseases in SCD:** Liver diseases in SCD can be divided into 2 groups.
  - **Those caused by Sickling process:**
    - Acute pain and jaundice
    - Acute hepatic sickle crisis
    - Hepatic sequestration crisis
    - Intrahepatic cholestasis
    - Benign hyperbillirubinemia
  - **Those resulting from disease complication and treatment**
    - Cholelithiasis and cholecystitis
    - Iron overload
    - Viral hepatitis
  - **Clinical Presentation:**
    - Striking Jaundice
    - Fever
    - Nausea And Vomiting
    - Right Upper Quadrant Pain, Tender Hepatomegaly
    - Bleeding Diasthesis
    - Hepatic Encephalopathy

        - Renal Impairment
        - Leucocytosis
        - Hyperbilirubinemia and Elevated Liver Enzymes.
        - Altered Coagulation Parametres
    - **Treatment:**
        - Can be disastrous / fatal
        - Prompt recognition and Early intervention with exchange transfusions and Intensive supportive care leads to favorable outcome

- **Acute severe anemia**: An acute fall in Hb may be superimposed upon the chronic anemia commonly caused by:-
    - Splenic sequestration crisis
    - Aplastic crisis
    - Hyper hemolytic crisis
    - Hepatic sequestration

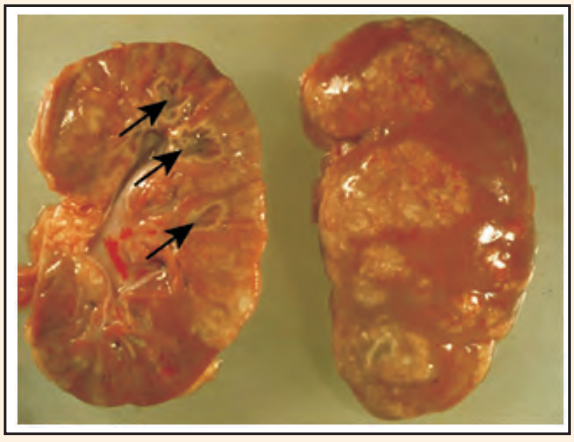
- **Splenic sequestration crisis**
    - Usually seen in children < 3 yrs
    - Present with
        - Abdominal pain
        - Tender splenomegaly
        - Sudden Fall of Hb >2 gm/dl below baseline
        - Raising reticulocyte counts because of vaso occlusion in spleen and pooling of massive quantities of RBCs
        - Risk of hypovolemic shock
    - Circulatory collapse and death can occur in less than 30 minutes
    - Associated with 10-15 % mortality, occurring before transfusions can be given
    - **Treatment**
        - Treatment of shock
        - IV fluids
        - Transfusions are required to maintain intravascular volume
        - Sequestration is recurrent in 50% of survivors
        - Splenectomy is usually recommended after the first event
        - Alternatively chronic transfusion therapy is used in children to delay splenectomy

- **Cerebrovascular disease in SCD:**
    - Central nervous system involvement is one of the most devastating aspects of SCD
    - May present with
        - Transient ischemic events (symptoms resolve in less than 24 hours) or Cerebral infarction (Common between the age of 2 to 9 & >29 years.)
        - Intracranial hemorrhage (Most frequent between age of 20-29.)
        - Silent infarcts leading to Cognitive and behavioral changes (like delay in learning ability, scholastic backwardness, memory loss)

- **Major Risk Factors include:**
    - Prior TIA.
    - Low steady state Hemoglobin level.
    - Rate of acute chest syndrome per year.
    - Increase steady state leukocyte count.
- **Therapy**
    - Acute therapy
        - Initial optimal therapy following a stroke in children-uncertain.
        - Exchange transfusion-more effective than simple transfusion in preventing second strokes.
    - Chronic therapy
        - Chronic transfusion prevention of recurrent stroke.
        - Incidence <10% when routine monthly PCV are given to maintain the Hb S fraction<30%.

- **PRIAPISM:**
  Priapism is a sustained painful penile erection in the absence of sexual activity or desire, lasting more than 2-4hours. When it is prolonged, it may lead to impotence
    - **Risk factors:**
        - Prolonged sexual activity.
        - Fever.
        - Dehydration.
        - Exposure to-
            - Alcohol
            - Marijuana/cocaine
            - Psychotropic agents
            - Sildenafil
            - Testosterone

- **Renal manifestations:**
    - Hematuria
    - Renal infarction & papillary necrosis.
    - Diminished concentrating ability.
    - Renal tubular acidosis.
    - Abnormal proximal tubular function.
    - Acute renal failure.
    - Progressive renal failure & Proteinuria.
    - Renal medullary carcinoma.
    - Urinary tract infection.



APLASTIC CRISIS

- Transient arrest of erythropoiesis usually triggered by parvo virus B 19 infection which completely prevents red blood cells production for 2-3 days.
- Acute worsening of the patient's baseline anaemia with markedly reduced reticulocyte count <1%

- Pallor, tachycardia, fatigue
- The condition is self-limited, with bone marrow recovery occurring in 7-10 days
- Most patients can be managed supportively but some may need blood transfusion

Cardiac involvement

Cardiac involvement is due to chronic anemia and microinfarcts. Hemolysis and blood transfusion lead to hemosiderin deposition in the myocardium and cardiomyopathy. Both ventricles and the left atrium are all dilated. Coronary Vasculature abnormalities are also common. Furthermore, a systolic murmur is usually present, with wide radiation over the precordium. Cor-Pulmonale may also develop from repeated Chest syndrome and Pulmonary hypertension.

Opthalmic menifestations:

The effect of sickle cell disease on the eyes comes from the increased viscosity, or "sludging," of blood and the narrowness of the eye's blood vessels. Proliferative Retinopathy is common and causes problems with vision. Sudden blindnesss may occur due to Retinal artery occlusions and retinal detachment.

TRANSFUSION THERAPY FOR COMPLICATIONS OF SICKLE CELL DISEASE

Red blood cell transfusions play an important role in the treatment of some acute illnesses in patients with sickle cell disease. For severe complications, timely transfusions may be life saving.

In general, appropriate use of red cell transfusions requires attention to the following issues:

Indications:

Indications for red cell transfusions include acute exacerbations of the patient's baseline anemia that require increased oxygen carrying capacity, acute life or organ-threatening vaso-occlusive episodes, and preparation for surgical or radiographic procedures that involve general anesthesia or the use of ionic contrast.

- Acute exacerbation of baseline anemia
    1. Aplastic crisis
    2. Splenic sequestration
    3. Hepatic sequestration
    4. Hyperhemolysis
- Severe vaso-occlusive events
    1. Acute chest syndrome
    2. Stroke
    3. Severe infection
    4. Acute multiorgan failure syndrome
- Preparation for procedures
    1. General anesthesia and surgery
    2. Radiographs with ionic contrast

Selection of transfusion products

Leukocyte-depleted, packed red blood cells are recommended. Where available, minor-antigen-matched, sickle-negative cells are preferred.

Transfusion method

A simple transfusion of packed RBC is appropriate for most situations . Partial exchange transfusion, may be needed for severe life-threatening illness or in situations where a relatively high baseline

hemoglobin precludes a simple transfusion that would risk hyperviscosity by increasing the hemoglobin level to > 10-11gm/dl.

Volume considerations

Simple transfusion with 10cc/kg of packed RBC typically raises the hemoglobin about 2gm/dl. Patients with severe anemia that develops over several days may be at risk for volume overload and congestive heart failure from rapid infusion of RBC. Thus, slow correction of the anemia (e.g. 4-5cc/kg packed RBC over 4 hr, often with furosemide) or isovolemic partial exchange transfusion may be needed to prevent precipitation of heart failure.

Hyperviscosity

Because sickle red cells are poorly deformable, simple red cell transfusions that increase the hemoglobin levels to>10-11gm/dl may cause hyperviscosity in patients not receiving chronic transfusions and should be avoided.

Hydroxyurea (HU):

The most significant advance in the therapy of Sickle Cell Anemia has been the introduction of hydroxyurea as a mainstay of therapy for patients with severe symptoms.

- **Indication of HU Sickle cell anemia**
  - 3 or more hospitalizations for VOC episodes in a 12 month calendar period
  - One or more acute chest crisis requiring transfusion
  - Significant number of days missed from school / work due to VOC pain managed at home regardless of number of hospital admissions
  - Abnormal TCD in patients refusing transfusion therapy
  - Chronic Hypoxia
  - Low Hb < 7 gms/100 ml

- **Investigations Before HU Therapy**
  - CBC with RC
  - Hb Electrophoresis or HPLC
  - LFT
  - RFT
  - S. LDH level
  - Hepatitis B,C and HIV serology Status

- **Dose initiation of HU**
  - Starting Dose : 20 mg/kg/day in a single daily dose orally
  - Increase dose by 5mg.kg/day every 8 weeks
  - Maximum Tolerated Dose (MTD) = 25-30mg/kg/day
  - Maximum permissible Dose : 35 mg/kg/day or 2 gm/day

- **Complication of Hydroxyurea**
  - Short term Safety and Toxicity
    - Headache, Nausea, Abdominal Pain
    - Skin Ulcers over leg
    - Hepatic and Renal Dysfunction
    - Transient and reversible myelosuppression
    - Reticulocytopenia

        - Long term Safety and Toxicity
            - Risk of Malignancy
            - Effect on Pregnancy and Fertility

- **Treatment summary of SCD**

    - Prevention of complications
        - Educate the patient/family about SCD.
        - Patients with sickle cell anemia should drink at least eight glasses of water everyday Take Diet with High calory and high protein foods. Folic acid is found in foods such as green leafy vegetables, fruits and grains.
        - Pain management strategies.
        - Evaluate by TCD (Trans Cranial Doppler).
          Anticipatory guidance for complication-splenic sequestration. Avascular necrosis and Acute chest syndrome.

    - Treatment of complications.
        - Folate supplements 1mg/day.
        - Infection control & prophylaxis-penicillin prophylaxis dose:<3years penicillin v125 mg 12 hourly orally.3-5 years penicillin vk 250mg 12 hourly orally.>5years can be stopped safely
        - Pain management.
        - Adequate hydration.
        - Avoidance/treatment of precipitating factor.
        - **Hydroxyurea.**

- **Immunizations in SCD:** Against –

    - Streptococcus Pneumoniae.
        - Conjugate Pneumococcal Vaccine.
    - Hepatitis B Virus.

- **Indication for blood transfusion**

    - **Acute transfusion** (keep Hct>30%)
        - Acute exacerbation of anemia (parvovirus B19 infection, Splenic sequestration)
        - Stroke or acute neurological deficit.
        - Acute chest syndrome.
        - Multi organ failure.
        - Pre-operative management.

    - **Long term transfusion.**
        - Primary & secondary stroke prevention.
        - Progressive organ failure.
        - Recurrent acute chest syndrome.

- **Infection:**

    - **Antibiotics.** Children with sickle cell anemia may begin taking the antibiotic penicillin when they're about 2 months of age and continue taking it until they're 5 years old. Doing so

helps prevent infections, such as pneumonia, which can be life-threatening to an infant or child with sickle cell anemia. Antibiotics may also help adults with Sickle Cell Anemia fight certain infections.

- **Immunizations to prevent infections**
  - All the Sickle Cell Disease children must be immunized against all vaccine preventable disease under UIP. These children must be immunized against pneumococcal vaccine also as pneumonia is the major cause of mortality in these children.

- **Guidelines for management of pregnant women with Sickle Cell Disease in Pregnancy:**
  - **Effects of Sickle Cell Disease in pregnancy:**
    - Maternal effects:
      - Acute painful crises in pregnancy
      - Acute Chest Syndrome (ACS)
      - Acute cerebro-vascular accidents
      - Acute anemia
      - Increased Maternal Mortality
    - Antenatal
      - ✓ Abortions, Poor weight gain, Pre-term labour, Pre eclampsia, Abruptio placentae, Inter current infections (pyelonephritis).

      Intra-natal
      - ✓ Dysfunctional labour, Hemorrhage and shock, cardiac failure.
    - Postnatal
      - ✓ Puerperal Sepsis, Sub-involution, Embolism
    - Fetal effects:
      - ✓ Risk of pre-maturity
      - ✓ IUGR (Intra Uterine Growth Restriction), LBW (Low Birth Weight), poor APGAR score
      - ✓ Risk of perinatal mortality
  - **Antenatal screening for SCD**:
    - ✓ Based on prevalence of the disease.
    - ✓ Partner screening
  - **Preconceptional care:**
    - ✓ Highly recommended for women with Sickle Cell Disease (SCD)
    - ✓ Assessment includes :
      a. Frequency of crises
      b. Previous blood transfusion needs
      c. Assessment of end organ damage
         i. Kidney – blood pressure and proteinuria,
         ii. Heart- echocardiography for Pulmonary Hypertension,
         iii. Fundoscopy for proliferative retinopathy,
         iv. For iron overload in women who have been multiply transfused in the past by serum ferritin levels

- ✓ If on antibiotic prophylaxis – continue it.
- ✓ Tab Folic Acid 5mg once daily
- ✓ Stop Hydroxyurea and Angiotensin –converting enzyme inhibitors before conception.
- ✓ Counselling :
  a. Role of dehydration, cold, hypoxia, overexertion and stress in frequency of sickle cell crises.
  b. How nausea and vomiting in pregnancy can result in dehydration and the precipitation of crises
  c. The risk of worsening anemia, the increased risk of crises and acute chest syndrome (ACS) and the risk of increased infection (especially urinary tract infection) during pregnancy
  d. The increased risk of having a growth-restricted baby, which increases the likelihood of fetal distress, induction of labour and caesarean section
  e. The chance of their baby being affected by SCD
  f. An up-to-date assessment for chronic disease complications.

■ **Antenatal care :**

- ➢ General aspects :
  - Multidisciplinary team approach – obstetrician, physician and haematologist.
  - Medical review by haematologist and assessment as described above in preconceptional care.
  - Avoidance of precipitating factors of sickle cell crises like exposure to extreme temperatures, dehydration and overexertion (avoid working in afternoon in the sun).
  - Early consultation and treatment for vomiting during pregnancy.
- ➢ Antenatal haemoglobinopathy screening:
  - Partner testing if it has not already been done.
  - If partner is a carrier – appropriate counseling early in the pregnancy (ideally by 10 weeks of gestation) to allow the option of first trimester diagnosis and termination if that is the couple's choice.
- ➢ Antenatal visits :
- ➢ 1st –
- ➢ Medication during pregnancy :
  - 5 mg of Tab Folic Acid daily
  - Maintain haematocrit at 30 percent
  - Continue antibiotics
  - Iron supplementation only if evidence of Iron deficiency anemia
  - Low dose Aspirin (75mg once daily) from 12 weeks of gestation to reduce risk of pre-eclampsia
- ➢ Additional care:
  - Frequent (monthly upto 12 weeks, fortnightly between 12 to 28 weeks and weekly thereafter) visits
  - Blood pressure and urine analysis at each consultation
  - Midstream urine for culture monthly

- Ultrasound examination :
  - Viability scan at 7-9 weeks gestation
  - 11-14 week anomaly scan
  - 16-20 weeks anomaly scan
  - Probably – Uterine Artery Doppler at 24-26 weeks for prediction of risk of pre-eclampsia
  - Serial fetal biometry every 4 weeks from 24 weeks
- Assessment of fetal wellbeing beyond 30-32 weeks:
  - Daily fetal movement charting
  - If fetal growth is normal – fortnightly modified biophysical scoring
  - If there is evidence of fetal growth restriction – weekly modified biophysical scoring with Doppler study

➢ Blood transfusion :
- No role of routine prophylactic blood transfusion in pregnant women with SCD.
- Indications of blood transfusion in pregnancy with SCD :

Indication	Comment
Women with previous serious medical, obstetric or fetal complications	Exchange or top-up transfusion
Women who are on transfusion regimen before pregnancy for primary or secondary stroke prevention or for the prevention of severe disease complications	Transfusion should be continued during pregnancy
Twin pregnancies	
Acute anemia	
Acute chest syndrome (ACS) or acute stroke	Prophylactic transfusion should be considered Top-up transfusion Exchange transfusion

➢ Mild pain during pregnancy :
- Can be managed at community level –
  - Rest
  - Oral fluids
  - Tab Paracetamol

➢ Refer to higher centre if :
- Pain does not settle with simple analgesia
- If febrile
- Atypical pain
- Chest pain
- Shortness of breath
- Acute abdominal pain during pregnancy :
  - Exclude ectopic pregnancy, placental abruption, pyelonephritis and appendicitis before considering as "sickle cell crisis"
  - Rapid assessment for medical complications – ACS, sepsis or dehydration needing critical care at tertiary centre

- If sickle cell crises –
  - multidisciplinary approach at higher centre with
  - appropriate analgesia,
  - intra-venous fluids (around 50mL/kg/24hrs) and
  - oxygen at the rate of 3L/min while
  - monitoring oxygen saturation (pulse oximetry)
  - Investigations – Full blood count, reticulocyte count, renal function tests (creatinine)
  - If needed – blood cultures, chest X-ray, urine culture, liver function tests, blood gas analysis etc.
  - Therapeutic antibiotics (broad spectrum) if evidence of infection
  - Partial Exchange transfusion
  - Thromboprophylaxis should be considered

➢ Other acute complications to be managed at tertiary level:
- Acute Chest Syndrome (ACS),
- Acute stroke and
- Acute anaemia

■ **Intrapartum care-**

➢ Site : At a hospital capable of managing high risk pregnancy

➢ Route of delivery: Pregnant women with SCD and normally growing fetus – normal delivery or VBAC (Vaginal birth after Caesarean section) if indicated.

➢ General measures :
- Blood should be kept ready
- Packed cell transfusion if haematocrit is less than 20 percent
- Women should be kept warm, adequately hydrated (oral and if necessary intra-venous) and should be given labour analgesia
- Antibiotic prophylaxis with broad spectrum antibiotics

➢ Specific measures :
- Maternal vitals
- Maternal Pulse oximetry to detect maternal hypoxia and institution of oxygen therapy
- Continuous intra-partum electronic fetal heart rate monitoring is indicated because of increased risk of fetal distress
- Avoid prolongation of labour
- Partial Exchange transfusion if needed

➢ Regional anaesthesia for CS if needed

Postpartum care -

✓ Testing of newborn for Sickle cell disease
✓ Maintenance of maternal oxygen saturation and fluid balance
✓ Routine postnatal care
✓ Contraceptive options :barriers, DMPA, Intra-uterine contraceptive devices, progestogen only pill

Sickle Cell Anemia Screening

Strategies adopted in Program:

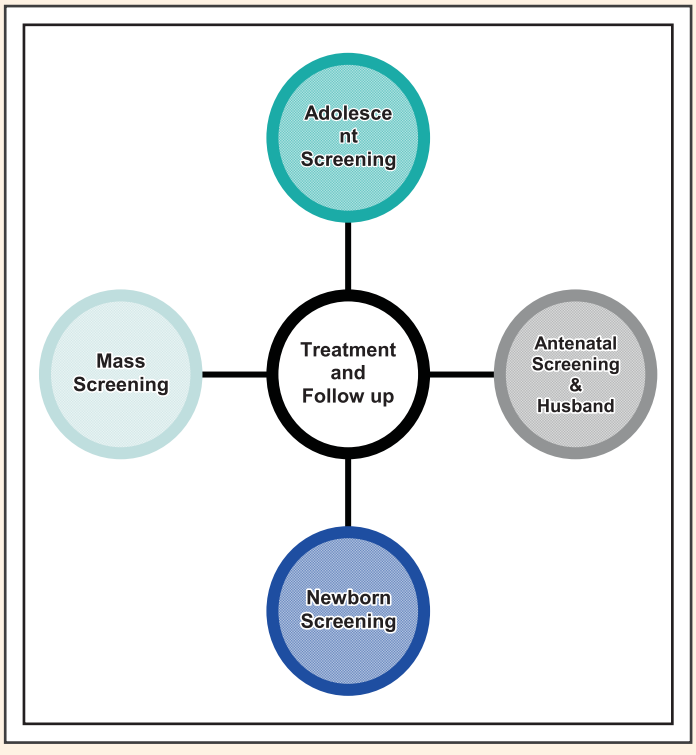
- Screening through specialized blood tests
  - ✓ Antenatal Screening of Eligible Tribal Couple
  - ✓ New Born Screening
  - ✓ Children, Adolescent and Mass Screening
  - ✓ Prenatal diagnosis
- Counseling
- Treatment and Follow up
- IEC/BCC

Screening is the basic need for the Sickle Cell Anemia control program. All the tribal populations have to be screened for Sickle Cell Anemia. Society has decided to take the screening program on mission mode to complete screening of all tribal population in next three years. Government of Gujarat has adopted the life cycle approach for Sickle Cell Anemia screening.

Life Cycle Approach:

The screening under this program covers the all age group from new born to old age people. The main target group for screening is the adolescents, antenatal and new borne. As this disease is a genetic in nature and there is no cure for this disease, prevention is the only way to keep away this disease. For this marriages between Sicklers and normal or two Sicklers have to be prevented. Therefore Government of Gujarat has adopted policy of screening of adolescents. So we can diagnose the sickle cell gene in pre marriage age and advise them to whom they should marry.

Our all Antenatal mothers in the tribal area are screened for Sickle Cell Anemia at "Mamta Divas"- a special immunization day in village. If mother is found positive for sickle gene, her husband is also screened. If husband and wife both found positive for sickle gene, they are advised for pre-natal diagnosis. If fetus is found to have sickle cell disease, legal MTP is advised. If Antenatal is not registered in early stage, then MTP is not allowed, fetus is delivered and new born screening is done from the blood spot taken from hill prick on filter paper.



All adults and geriatric persons are screened in mass screening camps held in community with the help of tribal development department.

Thus sickle cell anemia screening program covers the whole life cycle. This is the unique feature of the program.

Adolescent Screening:
All the adolescents in the tribal area should be screened for sickle cell anemia in mass screening campaign and in Mamta Taruni Divas. Blood sample will be taken and tested for sickling test (DTT test) in the field or at PHC center. All DTT positive samples will be sent for HPLC test at nearby HPLC testing center within 48 hrs in reverse cold chain in EDTA bulb.

HPLC testing center will send report in next 48 hrs to concerned block via email with cc copy to district nodal officer.

HPLC testing center will also issue the colour coded card and send the signed copy to the concerned block.

Antenatal Screening:
All the Antenatal mothers in the tribal area will be screened for Sickle Cell Anemia on Mamta Divas & Mamta Clinic. Blood samples will be collected at Mamta Divas and tested at field or at PHC center. Husband of the DTT positive Antenatal will be screened for Sickle Cell Anemia. Their blood sample will be collected within 24 hrs and tested for DTT. If husband is also found DTT positive his sample also will be sent to HPLC testing center along with DTT positive antenatal samples within 48 hrs in reverse cold chain in EDTA bulb.

HPLC testing center will send report in next 48 hrs to concerned block via email with cc copy to District Nodal Officer.

HPLC testing center will also issue the colour coded card and send the signed copy to the concerned block.

If husband and wife both are sickle positive, then prenatal diagnosis is advised. If fetus found to have sickle cell disease, then legal MTP advised.

New Born Screening:
All the New born baby in the tribal area will be screened for Sickle Cell Anemia. Blood sample will be taken on Guthrie Card by hill prick method. This Guthrie Card will be sent to Valsad Raktadan Kendra, Valsad for testing. Valsad Raktadan Kendra, Valsad will inform the report to concerned PHC and issue card accordingly.

Mass Screening:
Gujarat Sickle Cell Anemia Control Society has decided to finish the screening of all tribal population in next three years. Screening will be done in mission mode in all tribal districts with the help of Screening Agencies. The screening team will go to the village and do the screening of all tribals on fixed day in mass camp.

Counseling:

Counseling is most important part of the program. All the persons in the tribal community will be counseled first for the Sickle Cell Anemia before screening.

Sickle Cell Counselor will counsel all the Sickle Cell Trait and Sickle Cell Disease patients in details for their disease, possible crisis, and future pregnancy and for marriage also.

Laminated Color Coded Cards

All the Sickle Cell Trait and Sickle Cell Disease patients will be provided a color coded card according to their sickle cell status.

Normal Hemoglobin Card | Sickle Trait Card | Sickle Disease Card

Roles & Responsibilities

Counselor:

- Sickle Cell Counselor will have to maintain the record of total population, tribal population, screening details, No. of Sickle Cell Trait and No. of Sickle Cell Disease patients of area allotted to him.
- Counselor has to keep the line list of Sickle Cell Disease and Sickle Cell Trait of his/her area.
- He has to visit all the Sickle Cell disease patients every month and keep the record of their health status.
- He has to organize the counseling camp/ session for Adolescents, Antenatal and for community regularly.
- He has to keep record of crisis of all Sickle Cell Disease patients.
- He has to keep record of deaths due to Sickle Cell Disease.

Laboratory Technician:

- Laboratory Technician on PHC, CHC and DH has to do the DTT test for Sickle Cell Anemia.
- She/He has to visit Mamta Kendra and collect the blood sample of all Antenatal, Adolescents for Sickle Cell Anemia and do the DTT test.
- She/He has to check all the blood samples for DTT which are sent from the screening camp, Mamta Divas or Mamta Taruni Divas. All the samples have to be tested for DTT within 24 hours of the collection.
- She/He has to send all the DTT positive samples to designated HPLC center for confirmation with proper labeling in cold chain.
- She/He has to keep the record of Sickle Cell Screening of PHC area.

Medical Officer of PHC:

- PHC MO has to supervise all the screening activity of Sickle Cell Anemia.
- He has to fill the death audit form in case of death of Sickle Cell Disease patients.
- He has to send the report of Sickle Cell Screening, Sickle Cell Disease patients and financial progress every month to district level.
- He has to support the counselor for managing counseling session in PHC area.
- He has to supervise that all the samples collected should be tested within 24 hours of collection and all DTT samples should be reach the HPLC center within 24 hours.

District Surveillance Officer:

- District Surveillance Officer/ Epidemic Medical Officer will be the District Nodal Officer of the Sickle Cell Anemia Control Program.
- The overall responsibility for the implementation of the program in the district would be on him.
- He will collect the monthly report from block level and send it to state office regularly.
- He will monitor the overall activity of the Sickle Cell Anemia Control Program.
- He will co-ordinate with all NGOs in the district.
- He will visit at least 2% and cross check the death audit of sickle cell disease patients.

Female Health Worker:

- She will collect the blood sample of Antenatal mother and Adolescents on Mamta Divas and in the camp.
- She will keep the details of screening of Sickle Cell Anemia of her area.
- She will arrange to collect or collect the blood sample of husband of positive antenatal within 24 hrs of result.
- She will report any sickle cell crisis or death of sickle cell disease patients in her area to sickle cell counselor and PHC MO.s

Multi Purpose Health Worker:

- He will give the monthly quota of Tab. Folic Acid every month to all Sickle Cell Disease patients in his area.
- He will help the counselor in arrangement of counseling session in his area.
- He will report any sickle cell crisis or death of Sickle Cell disease patients in his area to sickle cell counselor and PHC MO.

Epidemic Branch
Commissionerate of Health, Family Welfare and Medical Services
Gandhinagar, Gujarat.
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