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Practicing Pearls for Sickle Cell Disease Management

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Practicing Pearls for Sickle Cell Disease Management

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Definition

- ☑ Sickle cell disease (SCD) refers to autosomal recessive group of disorders caused by qualitative mutations in the genes encoding for the beta-globin chain of the adult hemoglobin.
- ☑ This abnormal hemoglobin known as sickle hemoglobin (Hb S), on deoxygenation forms a polymeric structure resulting in deformed, rigid red blood cells leading to chronic hemolytic anemia and vaso-occlusion.
- ☑ It encompasses homozygous sickle cell anemia (SS), sickle cell/hemoglobin C (SC), sickle cell/β-thalassemia (S/β thal), and other compound heterozygous conditions such as sickle D-Punjab, sickle E-thalassemia, and sickle alpha-thalassemia.

Epidemiology

Sickle cell belt of India spans across states of Gujarat, Maharashtra, Madhya Pradesh, Chhattisgarh, West Bengal, Odisha, and Andhra Pradesh with the prevalence of heterozygotes ranging from 1 to 40% in many tribal populations.

Diagnosis

- ☑ Newborn screening
- ☑ High-performance liquid chromatography (HPLC) or Hb electrophoresis in a child with chronic hemolysis/pain crisis
- ☑ Genetic mutation analysis.

Pathophysiology and Symptomatology Profile

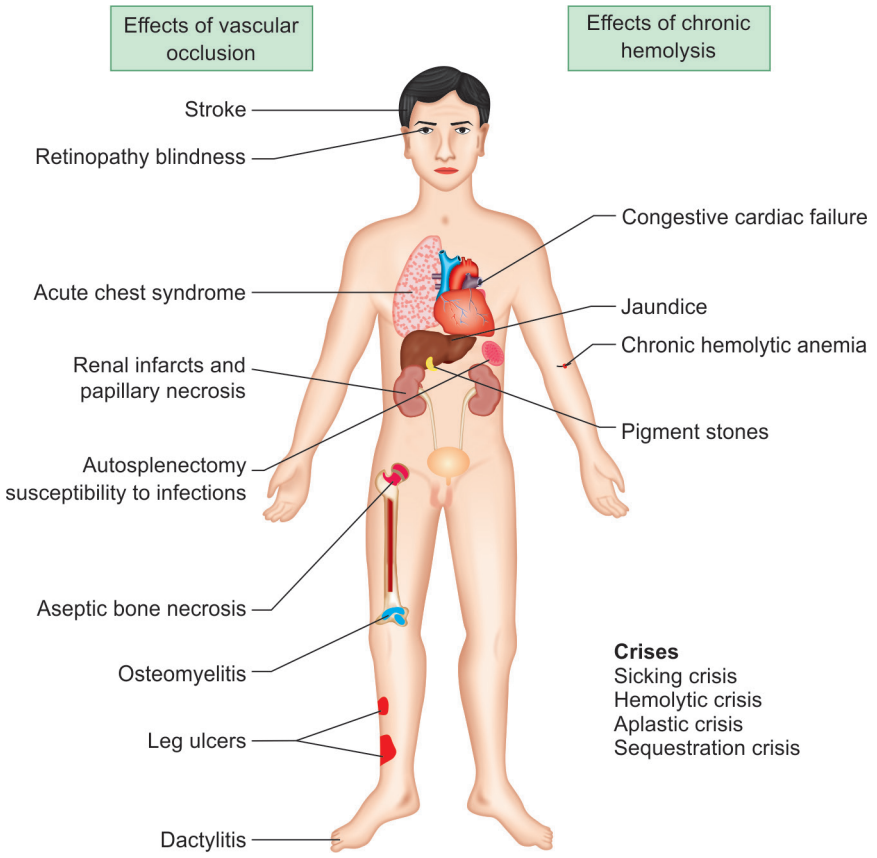


Fig. 1: Pathophysiology and symptomatology profile.

List of Investigations Required before Treatment

- ☑ Complete blood count (CBC) with reticulocyte count
- ☑ Extended blood grouping
- ☑ HPLC/Hb electrophoresis of patient and extended family
- ☑ Human immunodeficiency virus (HIV)/hepatitis B surface antigen (HBsAg)/hepatitis C virus (HCV)
- ☑ Renal function test (RFT)
- ☑ Liver function test LFT)
- ☑ Glucose-6-phosphate dehydrogenase (G6PD) test

Sickle cell disease should be considered as a chronic long-term and life-limiting condition with acute exacerbations that have far-reaching disabling consequences for the child and family. Hence, it requires a multidisciplinary and comprehensive teamwork to provide optimum treatment for health maintenance, acute care, and monitoring of disease-modifying therapy to SCD patients.

This team consists of pediatrician, hematologist, immunohematologist, intensivist, psychologists, social workers, etc.

Health Maintenance

Nonpharmacological Measures

- ☑ Parent education about disease, complications, treatment, and cure of SCD.
- ☑ Advise to maintain hydration.
- ☑ Avoid extreme cold, heat exposure, and heavy exercises.
- ☑ Diet rich in omega-3 fatty acids, vitamin A, and zinc may be advised.
- ☑ No role of vitamin C and E supplementation or sodium bicarbonate in routine management of SCD.

Immunization in Sickle Cell Disease

Apart from all routinely recommended vaccines, children with SCD must be administered pneumococcal (both conjugate and polysaccharide), *Haemophilus influenzae* B, meningococcal, and typhoid vaccines as per The Indian Academy of Pediatrics (IAP) guidelines.

Antibiotic Prophylaxis

- ☑ Oral penicillin V prophylaxis should be offered to all SCD patients starting from 90 days of life to 5 years of age **(Table 1)**.
- ☑ Continue prophylactic penicillin beyond 5 years of age if child has undergone a splenectomy or had an invasive pneumococcal disease.

TABLE 1: Age, dose, and frequency for antibiotic prophylaxis.

Age	***Dose***	***Frequency***
<1 year	62.5 mg	Twice daily
1–5 years	125 mg	Twice daily
>5 years	250	Twice daily

Role of Hydroxyurea in Sickle Cell Treatment

- ☑ *When to start treatment in SCD?*
  - The use of hydroxyurea (HU) is a mainstay in the overall management in SCD, since it reduces the incidence of acute painful episodes and hospitalization rates, and prolongs survival.

- In infants 9 months of age and older, children, and adolescents with sickle cell anemia (SCA), offer treatment with HU regardless of clinical severity.

☑ *What is the dose of HU?*

- Begin at 10–15 mg/kg/day single dose (round up to the nearest 500 mg). Monitor counts every 4 weeks initially to maintain absolute neutrophil count (ANC) > 2,000 and a platelet count > 100,000/mm^3.
- The dose may be escalated gradually to a maximum of 35 mg/kg/day if indicated clinically.
- In case of neutropenia and/or thrombocytopenia, withhold the drug, monitor the counts weekly till recovery and restart at a lower dose (5 mg/kg lower than the ongoing dose).
- Continue to monitor CBC, reticulocyte counts, RFT, and LFT quarterly once a stable or maximum tolerated dose is achieved.

Folic Acid

About 1–5 mg/day of folic acid is to be given to all children with SCD.

Indications of Blood Transfusion in Sickle Cell Disease ***(Table 2)***

TABLE 2: Indications of blood transfusion in sickle cell disease.

Acute conditions for blood transfusion	***Conditions for long-term transfusion therapy***
Acute clinical stroke	Primary/secondary stroke prevention
Acute chest syndrome	Recurrent acute chest syndrome
☑ Acute symptomatic anemia ☑ Parvovirus B19 infection ☑ Splenic or hepatic sequestration	Recurrent vaso-occlusive crises
Pregnancy	Pulmonary hypertension (PH)
Preoperative	Progressive organ failure

Iron Overload

☑ Patients on chronic blood transfusion therapy develop mainly hepatic iron overload. Cardiac and gonadal damage is uncommon in SCD.

☑ Serum ferritin can be used for monitoring iron overload.

☑ Liver iron concentration (LIC) can be measured by T2*MRI for patients > 10 years of age.

☑ Iron chelation should be initiated:

- After 10–12 transfusions
- Serum ferritin > 1,000 µg/L
- LIC > 7 mg/kg dry weight of liver

☑ Desferrioxamine (20–40 mg/kg/day) and deferasirox (20–40 mg/kg/day) are licensed for use in SCD.

Management of Acute Complications

BOX 1: Red flag signs to consult healthcare facility.

- ☑ Acute severe febrile illness
- ☑ Newly palpable spleen or increasing size of a previously enlarged spleen
- ☑ Significant respiratory symptoms (e.g., difficulty breathing, shortness of breath, severe cough, and chest pain)
- ☑ Severe abdominal pain, particularly if located in the right upper quadrant
- ☑ Neurologic symptoms, even if transient (e.g., facial droop or asymmetry, slurred speech, weakness or numbness in the arms or legs, and seizure)
- ☑ Priapism lasting >4 hours
- ☑ Significant increase in pallor, fatigue, lethargy, or jaundice
- ☑ Pain not adequately controlled by home medications

Acute Pain Crisis

- ☑ Assess the pain intensity using a visual analog scale (e.g., Wong–Baker faces scale).
- ☑ Identify and avoid factors that regularly trigger pain.
- ☑ Mild-to-moderate pain can be managed at home.
- ☑ Patients presenting to emergency should receive optimal pain relief within 30–60 minutes of admission.
- ☑ The longer the pain persists, the more challenging it is to control pain—use a step-down approach instead of a step-up one.
- ☑ Risk of opioid addiction should not be the ground to withhold opioids.

TABLE 3: Treatment of acute pain crisis.

Drug	*Dose*	*Comments*
Paracetamol	Oral 15 mg/kg/dose q6–8 hourly IV: 10 mg/kg/dose	Use with caution in hepatic dysfunction
Ibuprofen	Oral: 5–10 mg/kg/d	Use with caution in renal dysfunction
Codeine	Oral: 0.5–1 mg/kg/dose q4 hourly	Use with caution in hepatic dysfunction
Tramadol	IV/oral: 1 mg/kg/dose q8 hourly	Use laxatives liberally. Watch for respiratory depression
Morphine	IV/subcutaneous 0.1–0.2 mg/kg/dose q2–4 hourly	Use laxatives liberally. Watch for respiratory depression
Ketamine	IV infusion: 0.3 mg/kg/h	Maximum 1 mg/kg/h

Acute Febrile Illness

- ☑ Children with SCD are immunocompromised due to splenic hypofunction and are at risk of life-threatening infections, particularly with encapsulated organisms.
- ☑ Single oral temperature ≥100.4°F should be treated.
- ☑ A CBC, reticulocyte count, blood culture, and other specific tests should be done to look for focus of infection, e.g., chest X-ray in acute chest syndrome (ACS), X-ray local part for localized bone pain, etc.

- ☑ Empiric parenteral antibiotics are required in all children with SCD and fever.
- ☑ *Ceftriaxone*: 50–100 mg/kg/day IV (maximum 2 g) should be given within 1 hour of fever.

Clinical Stroke

- ☑ Can present with focal neurological deficits
- ☑ IV hydration and exchange transfusion to reduce Hb S to <30% of total hemoglobin.

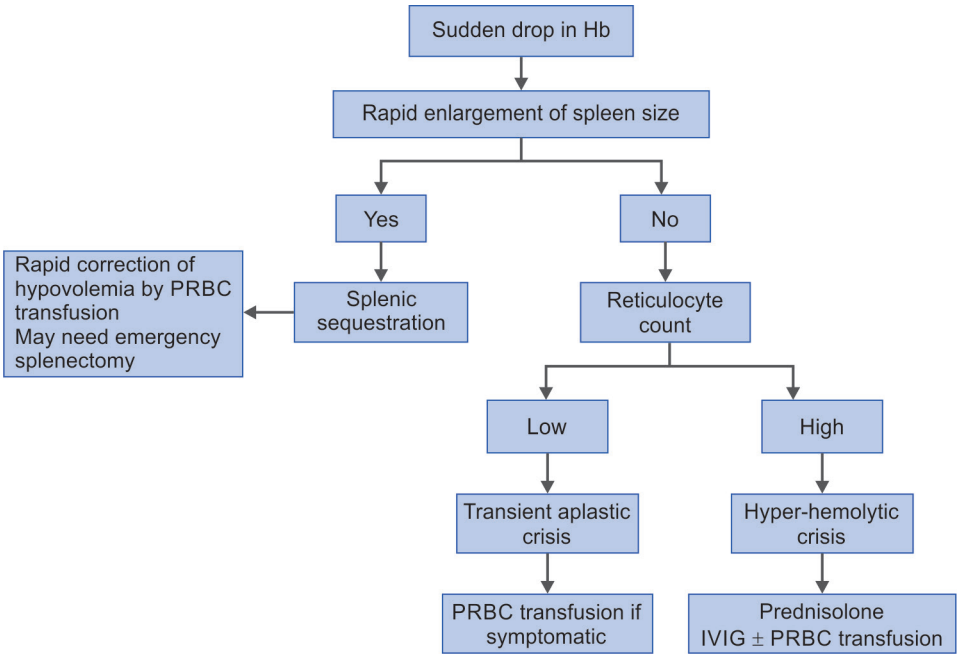
Acute Chest Syndrome

- ☑ *ACS presents* as fever, pain (chest, extremities, and ribs), and dyspnea with new radiodensity on chest X-ray can be triggered by infection.
- ☑ *Immediate management*:
  - Effective pain control
  - Adequate oxygenation to maintain a target oxygen saturation ≥ 95%
  - Empiric antibiotics—used regardless of whether fever is present (a macrolide plus a third-generation cephalosporin)
  - Blood transfusion/exchange depending on the hematocrit (to be done at a specialized center).

Acute Anemia

A sudden drop in Hb can occur due to transient aplastic crisis, hyperhemolytic crisis, or splenic sequestration.

Flowchart 1



(PRBC: packed red blood cell)

Curative Management

Hematopoietic stem cell transplantation is the only curative option for SCD patients as of today and should be offered only after a detailed discussion between pediatrician, hematologist, and a specialist transplant team with the family.

- ☑ Regular growth monitoring
- ☑ Monitoring of nutritional status
- ☑ Maintenance of pain crisis diary
- ☑ Regular palpation of spleen of older children.

TABLE 4: Parameters to monitor.

Investigation	*Frequency*	*Comments*
CBC with reticulocyte count	3 monthly	To see response of HU Monitor ANC and platelet count for HU side effects
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	For stroke prevention and screening
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
2D echocardiography	Low oxygen saturation and evidence of chronic lung disease	Screening for pulmonary hypertension
Urine analysis and specific gravity, urine albumin by creatinine ratio	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 liver	Annually	Evaluation of iron overload status
Ferritin	3–6 monthly	Evaluation of iron overload status
Retina screening	Annually 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

(ANC: absolute neutrophil count; BP: blood pressure; CBC: complete blood count; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HU: hydroxyurea; OPD: outpatient department; SCD: sickle cell disease)

Management

Role of Prenatal Testing in Sickle Cell Disease

Prevention of the disease can be done through carrier identification, genetic counseling, and prenatal diagnosis.

Indications of Tertiary Care Referral

- ☑ Acute and complicated sickle crises
- ☑ Routine comprehensive multidisciplinary care
- ☑ Genetic counseling
- ☑ Pregnancy.

Future Perspective

- ☑ *Crizanlizumab*: A monoclonal antibody against P-selectin prevents vaso-occlusive crises (VOCs) in SCD
- ☑ Voxelotor—HbS polymerization inhibitor
- ☑ Gene therapy.

Further Reading

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