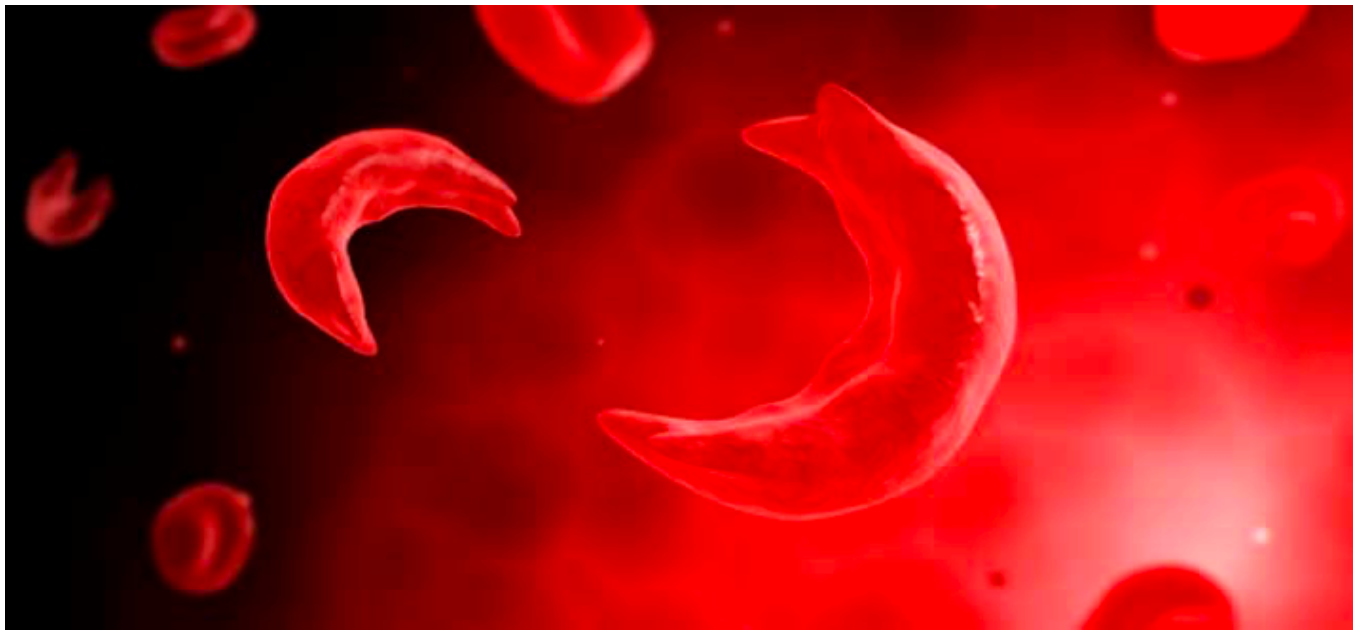
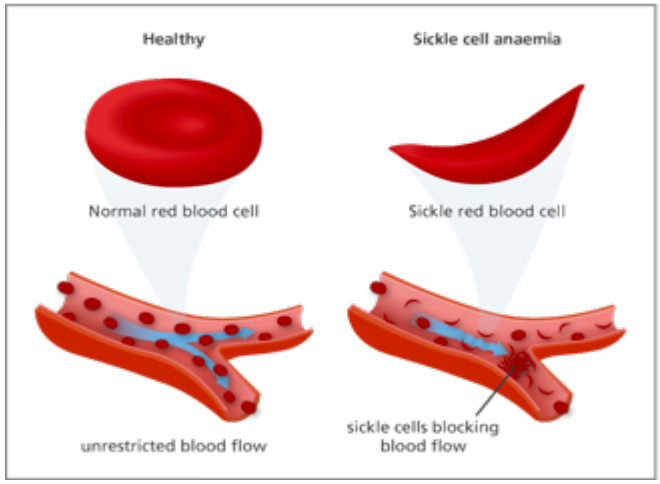
Resource Manual for the management

of the

Sickle Cell Anemia Disease





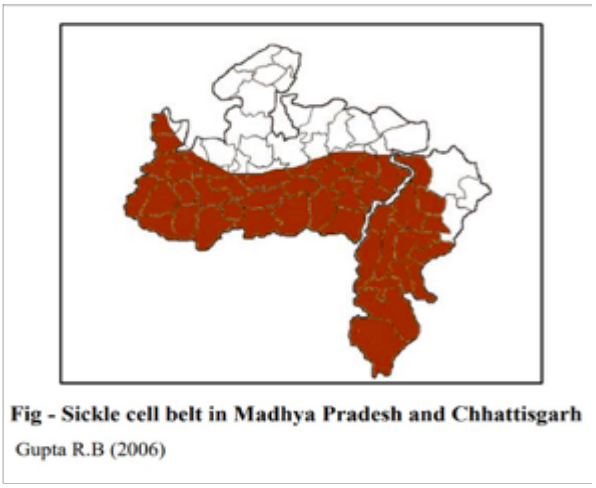


Fig - Sickle cell belt in Madhya Pradesh and Chhattisgarh

Gupta R.B (2006)

Jan Swasthya Sahyog, Ganiyari

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Prologue

Sickle cell disease is the major hemoglobinopathy seen in central India, inherited in an autosomal recessive fashion, and is responsible for a significant burden of illness and morbidity especially among tribals and forest dwellers where malaria is common. The prevalence of disease in these areas is due to survival advantage relative to normal individuals with HbA especially in early childhood.

Patients with this illness suffer acute painful complications such as acute chest syndrome, dactylitis, bone pain and bone infection, stroke and splenic sequestration crisis, since early childhood. Splenic dysfunction early on, leads to increased chances of premature death due to overwhelming infections. Those who are fortunate to survive into adulthood often have crippling avascular necrosis of the femoral head and sometimes head of humerus. Chronic pain, anemia, renal complications, stroke sequelae, retinopathy and pulmonary hypertension are the hallmarks of untreated patients who often suffer and die in silence and ignominy.

If only we as health care providers learn to suspect and screen for sickle cell disease and manage illness from an early age using simple principle and evidence-based practices, the lives of most of these patients can become pain free, with fewer hospitalizations and hence health care expenses and longer fruitful lives.

We hope this resource book enthuses many clinicians to take on this challenge to manage these patients effectively.

Jan Swasthya Sahyog team

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Chapter - 1: Introduction to the Sickle Cell Disease/Anemia

What is Sickle Cell Anemia? What is Sickle Cell Disease?

Sickle cell Disease/ Anemia is a type of hemoglobinopathy disorders. It is one of the most commonly found genetic or inherited disorders in the world. It is seen rampantly in the central rural India. RBCs which are usually circular, biconcave shape, become sickle shaped under stressful circumstances and cause obstruction in the blood vessels and hemolysis; thus, manifesting the symptoms of Sickle cell disease.

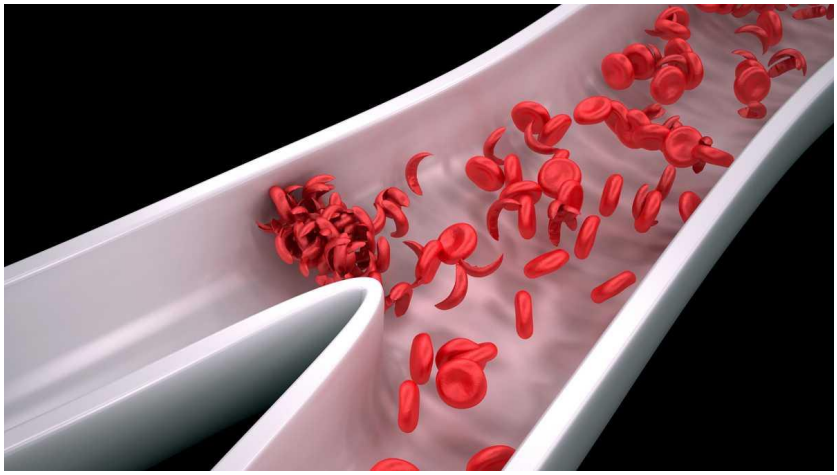
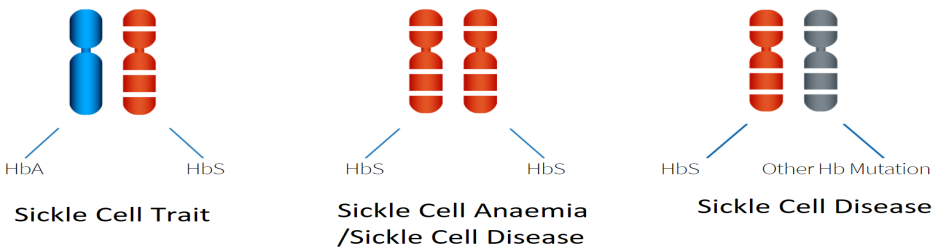


Diagram 1: Sickle-shaped RBCs causing an obstruction- Vaso-occlusion in the blood vessel

It is an inherited monogenic Hemoglobinopathy in which A to T single point mutation occurs on the 6th position of the Beta chain of hemoglobin; replacing Glutamic Acid with Valine ☒ $\alpha_2\beta_2{}^{6\ Glu☒Val}$. This is transmitted by an autosomal recessive manner.

Definitions:

Sickle cell anemia (HbSS) occurs when both beta globin alleles have the sickle cell mutation (βs).
Sickle Cell Disease refers to not only the patients with Sickle cell anemia but also to compound heterozygotes where one beta-globin chain allele includes Sickle mutation and the other beta-globin chain allele has mutation other than sickle cell mutation (βs) like β-Thalassemia, HbC, HbD, HbO^{Arab}.
When the sickle gene is present in the heterozygous form with only one beta carrying the sickle cell mutation and the other chain is normal; it is called Sickle Cell Trait- HbAS. It is carrier/trait/AS state for HbS and is not a form of Sickle Cell Disease. Sickle Cell Trait is generally considered harmless, under normal circumstances, and remains outside the definition of SCD.



We will discuss about SCD; its Pathophysiology and Epidemiology in this chapter.

Epidemiology:

Sickle gene is found predominantly in the tribal population of India, which located mostly in the forested hilly regions away from the mainstream. It is also prevalent in the Scheduled castes and other backward classes which are economically disadvantaged.

Introduction of Sickle gene in population was a part of the natural selection process for the people- most likely tribal people from forest dense region which were malaria-endemic. Sickle cell trait (AS) have relative resistance to Severe falciparum malaria; thus, it runs low parasite count by disabling the parasite to concentrate in the RBCs; thus, decreasing the risk of severe falciparum malaria. With consanguinity and the tendency of the population of getting married in the clan, the population was maximally affected by Sickle cell disease. Thus the distribution of SCD is well explained geographically where tribal population predominated.

FAQ 1: Is Sickle cell trait-AS as dangerous as Sickle cell Disease- SCD? Do Sickle trait people develop sickle disease eventually?
Trait - AS remains outside the definition of SCD, as discussed earlier. In sickle trait, the level of HbS is not enough to cause problems related to sickling except, with the trait, there may be painless hematuria due to medullary infarct. This condition does not occur in every patient with trait and does not lead to any life-threatening outcomes (% of ppl with hematuria & consequences). Sickle trait- AS people remain as trait throughout their lives and do not develop the disease at all.

FAQ 2: Are SCD patient's immune to malaria? Do SCD patients acquire malaria at all?
No. It's a myth. Sickle cell was a part of the natural selection process as Sickle cell Trait is selectively resistant "severe" form of Falciparum malaria. Even this selective resistance occurs maximally in the window period of early childhood where there is the transition between passive maternal immunity to active immunity. The length and the timing of this window period vary between communities and the pattern of malaria transmission. Sickle cell disease patients can develop any type or form of malaria; they are not immune to malaria.

Sickle cell disease is present worldwide with the majority of the patients in Africa, America and South-east Asia. (Figure 1). The Indian type of sickle cell disease has gene haplotype known as Arab-Indian haplotype.

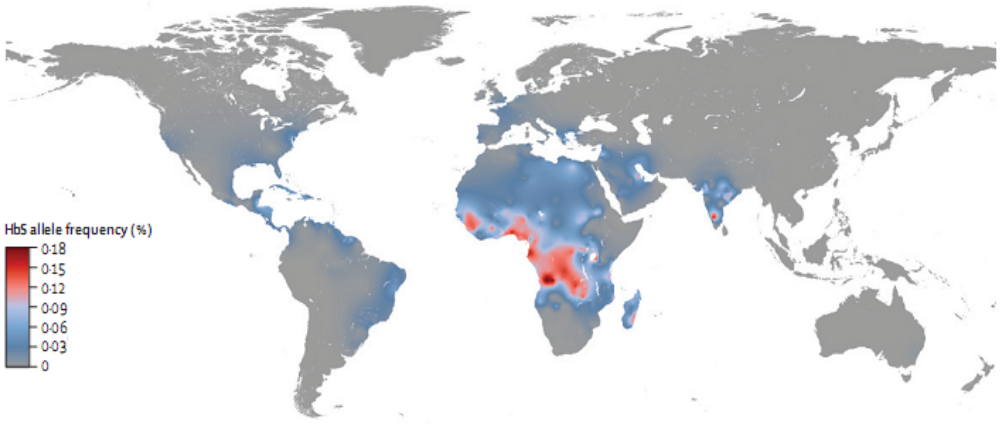


Figure 1: Worldwide HbS allele frequency

FAQ 3: SCD occurs only in the forested areas and is not a problem of people from cities?
Though sickle cell disease was predominantly found in the deeply forested areas affecting tribal population; with deforestation and migration of the population for daily wages, SCD is also found in the urban or suburban areas. As a medical professional, one should be vigilant and curious about the patient population one sees.

Pockets, where SCD is seen commonly, are - Maharashtra- eastern part, Gujarat – Southern part, Madhya Pradesh, Chhattisgarh, western Odisha, a small pocket in North Kerala and TamilNadu. Screening

programs for SCD have already started in Gujarat, Chhattisgarh, Madhya Pradesh, and Maharashtra on target-based approach. In Central India, some non-tribal communities also show SCD prevalence with the carrier/trait/AS prevalence being 2% -34%. (Figure 2)

FAQ 4: Sickle cell disease from India is not severe and does not require Hydroxyurea? Indians have higher endurance for pain, hence may not require analgesia or Hydroxyurea for pain crisis?

Sickle cell disease from India is ethnical of Arab-Indian haplotype, which is associated with more than 20% baseline HbF congenitally. Thus, old practice claimed lack of need for Hydroxyurea and decreased incidences of the pain crises as compared to the African-American literature. Many research papers published in India as well as internationally suggest that pathophysiology and course of the disease determine the severity and only the Haplotype is possibly associated with ethnicity. Any pain, in sickle cell disease, can beget the process of sickling and end in pain crisis. Hence, it is a MUST to provide analgesia for pain and prevent the crisis, it is necessary to provide Hydroxyurea. **It is unethical to deny the right of any SCD patients for Analgesia and Hydroxyurea, just based on anecdotal pieces of evidence.**

Prevalence of SCD among central India is 3.4%; with Madhya Pradesh has the highest load of SCD with 9,61,492 being sickle cell trait and 67,861 population being Sickle cell disease. Mostly the patients are of OBC followed by Scheduled Tribe followed by Schedule caste and General Category. 27 of the 45 districts in Madhya Pradesh fall under the sickle cell belt and the prevalence of the HbS gene varies from 10 to 33 per cent. It has also been estimated that 13,432 pregnancies would be at risk of having a child with sickle cell disease in this State and the expected annual births of sickle homozygotes would be 3358. (figure 3). Thus, the approximate prevalence of SCD in Madhya Pradesh is 0.9 to 1.2% of the total population.

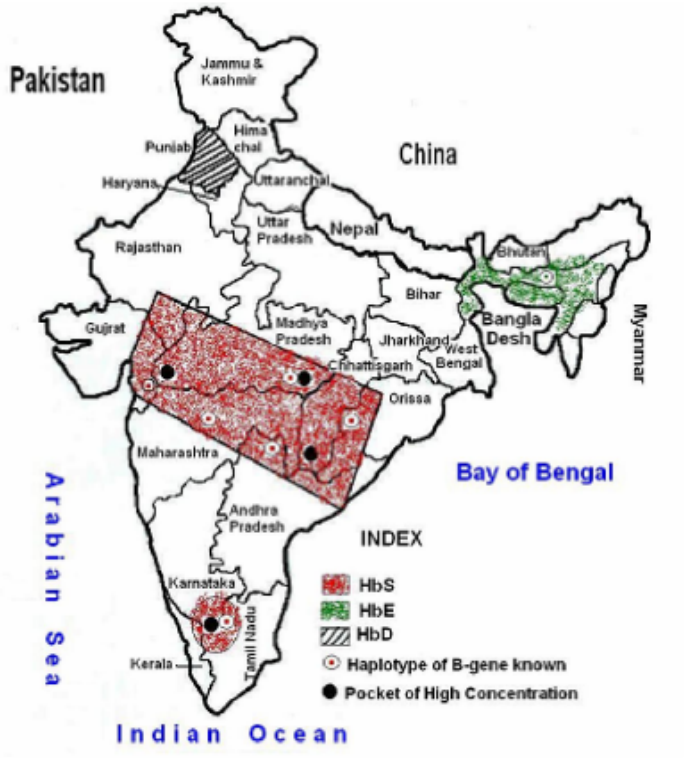


*Fig - Distribution of hemoglobinopathies in India**

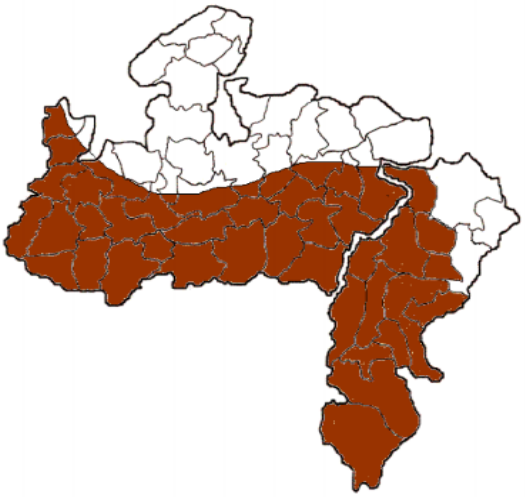


*Fig - Sickle cell belt in Madhya Pradesh and Chhattisgarh **

*Source of both Pictures - Gupta R.B(2006)

Inheritance of Sickle Cell disease:

As noted earlier, SCD is transmitted in an autosomal recessive manner; thus, the disease is manifested only when it is present in the homozygous state- SS, in combination with one sickle beta-globin chain allele which has beta-globin chain mutation like β^0/β^+ Thalassemia, HbC, HbD, etc.

Following possibilities might occur [This chart is also known as Sickle Kundali (सिकल कुंडली)]:

= AA / Normal / Non-Sickle / बिना सिकल / सामान्य

= AS / Trait / Carrier / सिकल वाहक / सामान्य

= SS / Patient / Diseases / सिकल रोगी

If both parents are AA then there would be:

- 100% chances that in every pregnancy baby would be AA.

Note: This type of marriage is preferable.

If one parent is SS and one parent is AA then in every pregnancy there would be:

- 100% Chances of having AS baby

Note: This type of marriage is preferable.

If One parent is AA and Another is AS then in every pregnancy there would be:

- 50% chance of having AA baby &,
- 50% Chances of having AS baby.

Note: This type of marriage is preferable.

If one parent is SS and second is AS then in every pregnancy there would be :

- 50% chance of having SS baby &,
- 50% chance of having AS baby.

Note: This type of marriage should not be preferred.

If both parents are AS then in every pregnancy there would be :

- 25% Chances of having SS baby,
- 50% chances of having AS baby, &
- 25% chances of having AA baby.

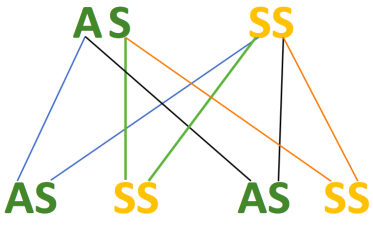
If both parents are SS then:

- It is 100% sure that all their children are going to be SS (Patients).

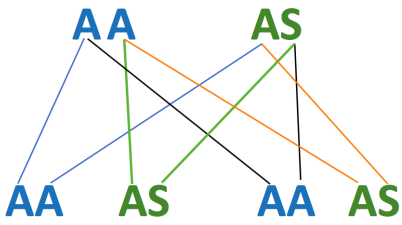
Note: This type of marriages should be avoided to reduce the burden of the family in the future.

Now using the following chart let's understand how the genes are getting transferred in the above chart:

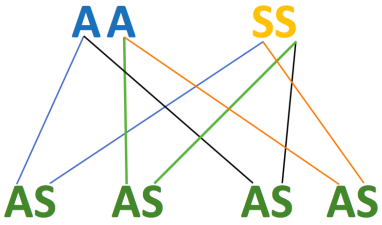
1. One parent Trait & another patient



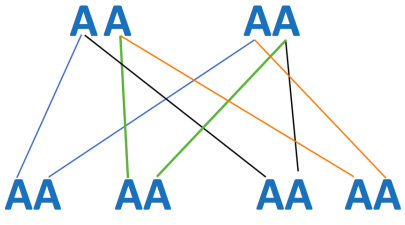
2. One parent Normal & another Trait



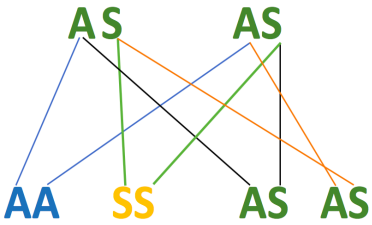
3. One parent Normal & another Patient



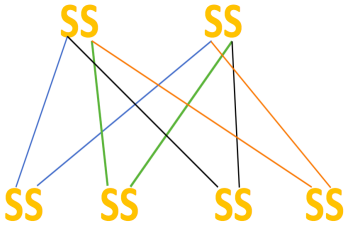
4. Both Parents Normal



5. Both parents Trait



6. Both parents are patients



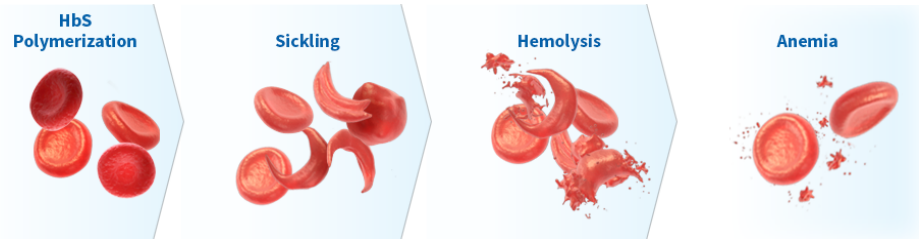
If there are chances of having a diseased baby (SS) then in such cases marriage or the conceiving the pregnancy should be avoided.

FAQ 5: For a couple with both parents being carrier/trait- AS; if their first child has Sickle cell disease; the chances of having SCD in 2nd child are none?

There are 25% chances of having SCD in EVERY pregnancy outcome for parents with a trait. Screening of newborn is necessary to detect the genetic status for SCD early. Thus, even if the first child has SCD, there are 25% chances that the 2nd child might have the disease.

Pathophysiology of Sickle cell Disease:

In Sickle cell disease, under usual circumstances, the RBCs retain their circular, biconcave shape. But, under stressful conditions like cold, dehydration, hypoxia, high temperature (fever), infections, where oxygen consumption is high and deoxygenated hemoglobin predominates, the RBCs change their shape to sickle. Thus, such sickle-shaped RBCs are less pliable to traverse the blood vessels, thus they either get obstructed in the vessels or hemolysis. Such sickled RBCs show "Co-operative phenomenon" and form a chain of RBCs- polymers. Minimum 10 sickled RBCs are required for the formation of polymers. The usual lifespan of the sickled RBCs is reduced to 10 – 20 days. Thus, Anemia is apparent.



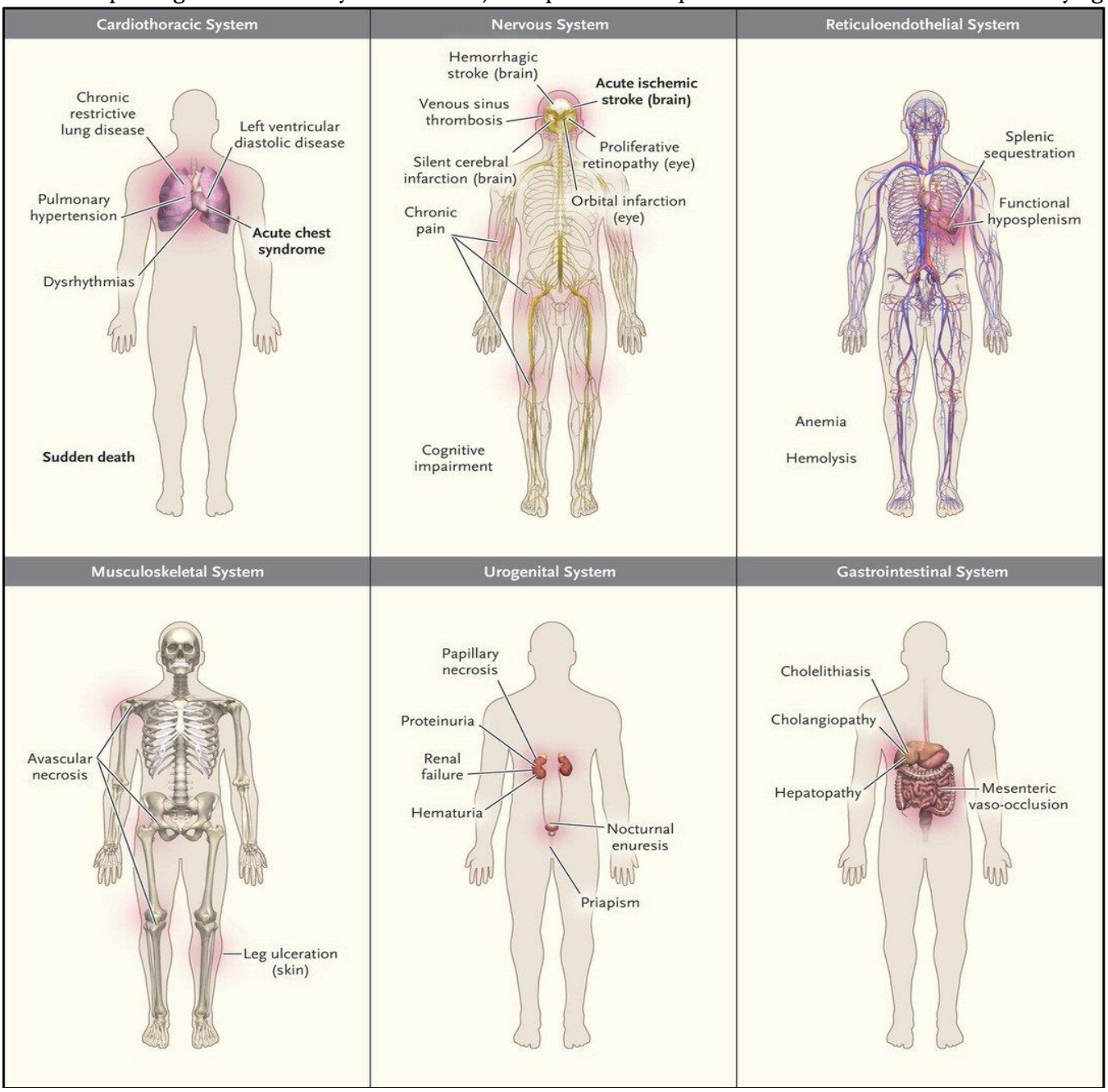
Picture: Mechanism of the Hemolysis

Thus, SCD manifests clinically by following two pathological processes:

1. Vaso-occlusion:

- Vaso-occlusion can occur in minor as well as major vessels anywhere in the body, eg. Bone, joints, lungs, abdominal organs, brain, spleen, kidneys etc. (Diagram 1)

- Vaso-occlusion is manifested clinically as pain at the site where occlusion occurs. Vaso-occlusion further leads to hypoxia due to non-availability of blood, thus propagating the process of sickling in forward direction.
- When vaso-occlusion occurs in the spleen, leading to infracts, auto-splenectomy occurs, thus impairing the immune system. Hence, SCD patients are prone to severe infections at an early age.



Picture: Pathophysiological manifestations

2. **Hemolysis:**

Due to polymerization of sickled RBCs, hemolysis occurs which is manifested as

A. Anemia => which may be severe
B. Jaundice which may be continuous (Variable) => Manifested as yellowish discoloration of skin or eyes, which may be continuous when hemolysis occurs.

Chapter - 2: Interpretation of Investigations in sickle Cell Disease

Ordering and Interpretation of labs is an important skill in sickle cell disease.

Overview of blood tests for anemia:

- Hemoglobin –

for the severity of anemia. Blood transfusion is recommended for Hb less than 5gm/dl even without symptoms and less than 7gm/dl with symptoms. In an acute crisis or during pregnancy, Hb should be maintained around 10 gm/dl.

Caution: During Acute episode patient may be dehydrated and Hb is falsely high so it is good to repeat Hb on next day after correcting dehydration.

- Total leucocyte count -

Increased - bacterial infection, usually seen in acute presentations, increased counts may also be due to inflammation due to infarction secondary to blockage of vessels or due to dehydration which needs clinical judgement.
Reduced - aplastic crisis.
Leukopenia, neutropenia, and/or thrombocytopenia may signify abnormal bone marrow function or increased peripheral destruction of blood cells.

- Retic Count:

Reticulocytes are immature RBCs and their count indirectly indicates, the functioning of marrow cells.

Pancytopenia with low reticulocyte count indicates bone marrow suppression. Causes of bone marrow suppression/failure include drugs or toxins, nutritional deficiency folic acid or vitamin B12 deficiency, acute leukemia, or aplastic anemia.
Pancytopenia with increased reticulocyte indicates increased peripheral destruction of red blood cells. Increased peripheral destruction of blood cells may be due to splenic hyperfunction ("hypersplenism"), microangiopathic hemolytic anemia (e.g., hemolytic uremic syndrome).

- Differential count:
  - ❏ provides information about the nature of the infection.
  - ❏ Increased neutrophils of more than 80 %, usually seen in bacterial infections.
  - ❏ Increased lymphocytes of more than 35% seen in viral infections.

- Peripheral Smear:

RBC size – It is usually commented compared to the size of small lymphocyte on smear as micro (smaller than small lymphocyte) or macrocytosis (larger than small lymphocyte). In automatic cell counters, MCV (mean corpuscular volume) gives RBC size.

Microcytosis - Iron deficiency anemia, Thalassemia, Anemia of chronic disease, copper deficiency (very rare)

Macrocytosis - B 12 deficiency anemia, folic acid deficiency anemia.

Mixed micro and macrocytosis - Mixed nutritional deficiency iron and folic acid/B12 deficiency anemia.

MCV - mean corpuscular volume is average volume of red blood cells, calculated by automatic cell counters by averaging size of blood cells. Normal values vary as per cell counters. In sickle cell disease, baseline MCV should be recorded and subsequently after starting hydroxyurea, MCV should increase gradually and one should aim at a value of more than 100 fl or Hb of more than 10 Gm% as an upper limit for hydroxyurea up-titration.

- ⇒ Sickle cells as seen in sickle cell disease; especially fixed sickle cells are of diagnostic importance.
- ⇒ The presence of numerous nucleated RBCs indicates rapid bone marrow turnover and is seen with hemolytic processes.
- ⇒ Hyper segmented neutrophils suggest vitamin B12 or folate deficiency.
- ⇒ Early white blood cell forms (e.g., blasts) along with anemia should raise the suspicion of leukemia or lymphoma.

SGPT (ALT):

SGPT/ALT is a liver enzyme normally located in liver cells and spills out in blood only when liver cells are damaged.

Creatinine:

Creatinine is a toxic substance formed in the body after the metabolism of protein, it is excreted by the kidney in the urine. Its value when increased indicates deficient renal function.

Uses of lab tests in sickle cell disease:

D. To monitor treatment
E. For identifying complications (usually for patients presenting in emergency)
F. For diagnosis of sickle cell disease

A. To monitor treatment

1) Hb, TC, DC, Platelet:

After starting hydroxyurea, initially Hb, TC, Platelet count should be repeated within 2-4 weeks to diagnose bone marrow suppression due to hydroxyurea which is seen rarely. Gradually monitoring frequency is reduced to 3 monthly based on patient's willingness for follow up.

2) MCV:

Baseline MCV should be recorded and subsequently after starting hydroxyurea, MCV should increase gradually and one should aim at a value of more than 100 Fl or Hb of more than 10 Gm/dl as an upper limit for hydroxyurea up-titration.

3) SGPT:

If available within the facility, SGPT can be monitored in initial 3-4 visits and afterwards once patient tolerates hydroxyurea well, SGPT testing is required only when patient has symptoms of hepatitis.

B. For identifying complications (usually for patients presenting in emergency)

Additional investigations to diagnose complications based on clinical assessment are listed below.

1) Pulmonary Arterial Hypertension-
    - CXR-Positive Findings-Prominent PA segment, absence of vessels in lateral lung zones
    - ECG: Positive findings: Tall P waves in lead II s/o P pulmonale
    - Echo- Elevated pulmonary artery pressure

2) Osteomyelitis-
    - ESR- High ESR usually more than 40 indicates bone osteomyelitis and could be useful to differentiate between vaso-occlusive crisis and osteomyelitis.
    - X ray of the bone

3) SCD with infection-
    - For patients presenting with fever usual tests should be done to diagnose etiology of fever similar to other patients.

4) Stroke-
    - RBS to diagnose hidden hypo or hyperglycemia.
    - Lumbar Puncture after carefully ruling out papilledema and thrombocytopenia for possible TB meningitis, Encephalitis if clinically suspected.
    - CT Brain- non-contrast (contrast only if space occupying lesion seen) for diagnosing nature of stroke-ischemic or hemorrhagic.

5) Avascular Necrosis -
    - X ray of pelvis including both hip joints.

6) Acute Chest Syndrome-
    - CXR-PA view

7) SCD with pregnancy-
    - Close follow up and monitor Hb at least every monthly and blood transfusion if Hb less than 10 Gm/dl.

8) Priapism-
    - Doppler study to diagnose blood flow obstruction.

9) Sickle Nephropathy-

- Urine albumin,
- Serum creatinine,
- Calculation of creatinine clearance,
- USG for Kidney size and shape

10) Sickle Hepatopathy-

- SGPT,
- Serum Albumin,
- PT,
- INR,
- Bilirubin-total and direct.

C. For diagnosis of sickle cell disease:

⇒ Hb, TC, DC, Platelets - One can suspect sickle if these tests show unusual results.

⇒ Baseline SGPT - only if available in the facility.

⇒ Peripheral Smear- look for fixed sickle cells in the smear.

Baseline Tests

1. Reticulocyte Count
2. Sickle Prep test - Slide Method
3. Solubility Test - Screening Test

Screening Tests

4. Hb Electrophoresis test
5. HPLC based on availability in the lab.

Confirmatory Test

For suspected Complications: as mentioned above if a patient presents with some complication.

1) Reticulocyte Count

Reticulocytes are immature but already anucleate erythroid cells with residual amount of RNA. In healthy individuals' reticulocytes are in the bone marrow for about 3 days and spend 1 day in circulation before they mature into an RBC. Under steady state conditions, RBC production equals RBC losses. With worsening anemia and increase in erythropoietin stimulation, the bone marrow releases reticulocytes at an earlier stage in their maturation and reticulocytes are in the peripheral circulation for a longer time. The reticulocyte count is therefore useful as a marker to estimate the degree of erythropoiesis and the appropriateness of the bone marrow response to anemia. Since sickle cell anemia is a chronic anemia, the reticulocyte count will be elevated at baseline and it is important to measure when there is a drop in the hemoglobin to make sure the bone marrow is responding adequately.

Principle:

Brilliant cresyl blue is an isotonic medium which selectively stains nucleic materials of reticulocytes which can be seen under a microscope.

Equipment Required:

i. Slide
ii. Test tube
iii. Retic Reagent
iv. Microscope

Sample: EDTA Sample/Whole Blood

Procedure:

1. Take 200µl blood sample in 5 ml glass test tube.
2. Add 100µl retic stain (2:1), mix and incubate at 37°C for 20 minutes .
3. Prepare few smears in microscopy glass slides.
4. Report in 100x, oil immersion lens.

Reporting:

In Brilliant Cresyl Blue Stain under oil immersion lens nuclear material in reticulocytes appear in dark blue color and cytoplasm in blue color.

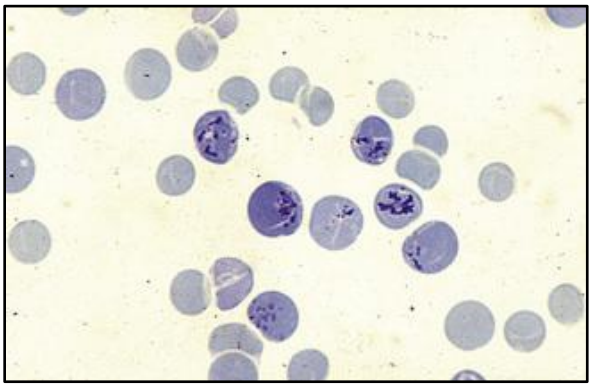


Fig: Reticulocytes in Brilliant Cresyl Blue Staining

Calculation:

Retic Count = ; Normal Value: 0.2-2%

Reagent Preparation:

A. Na2 HPO4. 2H2O (Concentration = 23.4gm / liter)
B. Na2 HPO4 (21.3gm / lit

Quantity of reagents: (A = 64ml) + (B = 36ml) = 100ml (pH 6.5)
25ml+ 250mg Brilliant Cresyl Blue or New Methylene Blue

Quality Control:

The performance of stain must be periodically checked by known samples. Accuracy of reporting reticulocyte count is subject to the professional experience of each person as well as the use of a good optical system that could make clear magnification of the cells from smear.

2) Sickle Prep Test (Slide Method):

Principle:

RBCs become sickle shape in Sickle cell disease. Due to its oxygen carrying nature, sickle shape RBCs also appear in normal RBC shape on routine microscopy. The sickle shape appears only in deoxygenated sickle RBCs. In Sickle prep method, sodium dithionate helps in deoxygenate the RBCs. Wax sealing prevents further air/oxygen contact of RBCs, thus sickle RBCs remain in sickle shape. These can be easily identified on microscopy. De-oxygenation with sodium dithionate takes about an hour. In sickle prep investigation, blood sample is subjected to de-oxygenation after sealing the sample with wax followed by microscopy to identify sickle RBCs.

Requirement:

- Slide
- Sickle buffer
- Cover slip
- Wax
- Match box
- Dropper
- Lancet
- Needle
- Spirit
- Bunsen Burner
- Electronic balance

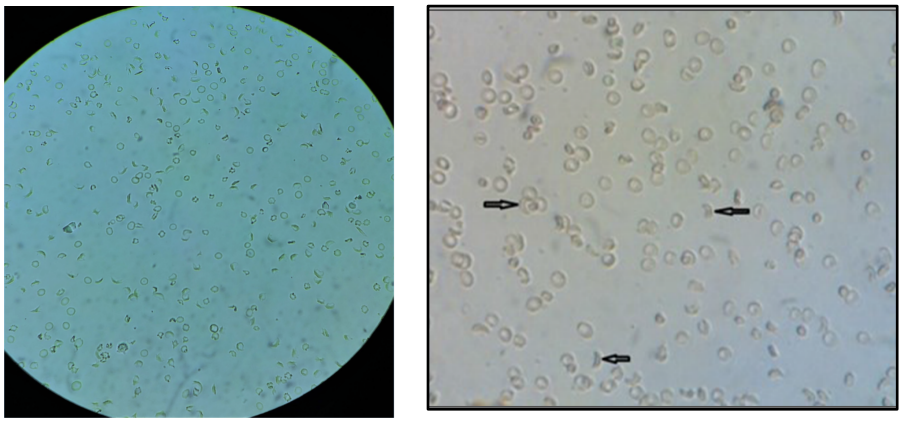


Fig: Sickle Prep Test Slides

Chemicals required:

- Disodium hydrogen phosphate (Na2HPO4)
- Sodium dithionate (Na2S2O4)

Process of making buffer and working solution:

Buffer: Mix well -Disodium hydrogen phosphate (Na2HPO4) - 8.1 grams and distilled water 833 ml. This mixed solution can be kept in dark brown bottle for 4-5 month.

Working Solution: Mix well a solution of 12.5 ml of buffer and 110 mg sodium dithionite (Na2S2O4) in a screw cap test tube. This working solution can be stored in refrigerator up to a week.

Process of sickle prep testing:

1. Place a small drop of blood(5µl), EDTA sample/finger prick in the middle of a microscopy slide and add a drop of working solution on the sample. Mix Well.
2. Cover this mixture with a cover slip. Be careful in placing the cover slip, no air bubbles should be present in the mixture after cover slip is placed on it.
3. Seal the coverslip border with liquified wax.
4. Observe the slide under 40X zoom of microscope after 1 hour.
5. If sickle test is positive - we would find sickle shaped red blood cell (as marked in the slide here). In case of negative sickle test, there would be no change in RBC shape.

Precautions:

- Heat the wax only until it liquefies. Do not heat it in high temperature. Using very hot wax for sealing will affect results

- For making working solution, be very particular of using 110mg strictly. Higher quantity can crenate RBC's resulting in false positive results.
- Avoid using more than 5µl blood for slide preparation, this will cause overlapping of RBC's and affect reporting of results.

Quality Control:

To check if the working solution is giving correct result, make a sickle cell preparation for known sickle positive sample with a freshly made working solution. After one hour if the RBC's in the preparation appear sickle shaped then we can go ahead with using the solution for testing other samples. IF, NOT then discard the working solution and make a fresh one again and repeat quality check. Every time the working solution is made, quality control should be done before proceeding with sickle preparation for other samples. Once working solution is made it is usable for maximum 12 hours.

Caution: Sickling test result is read after 1 hour (early) and after 24 hours(Delayed) and sickling is considered negative only after "Delayed" (24 hour) result is negative.

3) Solubility test

Principle:

Solubility test for detection of Hemoglobin S is based on the solubility difference between HbS and HbA in concentrated phosphate buffer solution. In this test RBC'S are lysed by a hemolytic reagent and the released hemoglobin is then reduced by sodium dithionite in a concentrated phosphate buffer (R_1). In the presence of sodium dithionite, HbS precipitates causing turbidity of the reaction mixture. HbA and other hemoglobin's are soluble and hence a transparent solution is seen. A positive result is indicated by a turbid suspension through which the ruled lines are not visible. A negative result is indicated by a transparent suspension through which the ruled lines are visible.

Reagents:

- Solubility Buffer (Phosphate buffer) (R1)
- Hemolytic Agent (Sodium dithionite powder) (R2)

Preparation of working buffer:

1. To Prepare working buffer add given quantity of Hemolytic agent(R2) in the bottle of solubility Buffer (R1) and mix it well. (Note: Quantity & bottles come with the solubility kits).
2. Let it stand for 10 minutes.
3. Mix the reagent thoroughly before use.

Sample required:

2 ml EDTA sample

Method:

1. Label test tube appropriately, add 2 ml of working reagent to each tube.
2. Note down the Hb value of the sample.
3. If Hb>8 gm/dL Add 20µl of whole blood sample. If Hb < 8 gm/dL add total 40µl whole blood sample.
4. Mix well and allow to stand for 10 minutes.

5. Read the turbidity in the test tubes by holding the tubes against a dim illumination and viewing the black lines printed on a paper.

Iinterpretation of Results:

1. A turbid solution(black lines on background of result reading stand are barely visible and cannot be seen) indicates a positive result for sickle cell.
2. A clear solution (black lines on background are clearly visible) indicates a negative result for sickle cell.

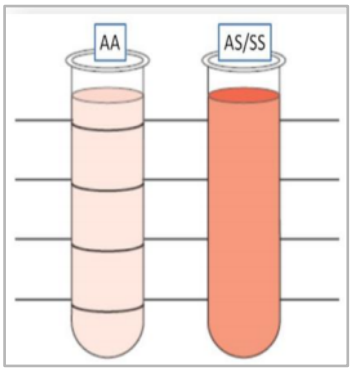


Fig - The Sickle cell solubility test

Quality Control:

⇒ After preparation of working reagent do solubility test on known positive and negative sample for sickle cell before proceeding with other samples.

⇒ If hemoglobin concentration is 7g/dl or less, the sample volume for testing should be doubled to 40µl in screening method.

⇒ False negative results may occur in infants under 6 months of age due to high levels of hemoglobin F.

4) Hb Electrophoresis (Hemoglobin Electrophoresis by Agarose gel Method)

Principle: Hemoglobin molecules dissolved in water are electrically charged. The magnitude of the charge and its polarity (positive or negative) are determined by the kind of hemoglobin and by the acidity or alkalinity of the solution. In an electrical field, charged hemoglobin molecules move towards the cathode or anode depending on the polarity of the charge and for the molecules having the same polarity of charge, the speed of movement depends on the magnitude of the charge. Because of differences in speed, different kinds of hemoglobin molecules in a mixture migrate different distances in a given span of time and get separated in discreet migration fronts that appear as bands on the electrophoresis medium (agarose gel or cellulose acetate paper).

For example, in a mildly alkaline medium (pH 8.2 or 8.4), normal adult hemoglobin (HbA) and sickle hemoglobin (HbS) both move towards the anode but HbA moves faster leaving HbS behind. Ultimately all the HbA molecules accumulate in a distinct band ahead of the HbS molecules, which also move together in a trailing band.

The different bands can be identified by comparing their positions with those obtained from control samples of known varieties of hemoglobin. These can also be clearly visualized and identified on an agarose gel stained with Amide black 10B Stain.

Caution: Sample for Hb Electrophoresis should be collected before blood transfusion or 4 months after previous transfusion so as to avoid false readings due to transfused blood.

Materials needed are:

- Electrophoresis unit with power supply
- Weighing Machine
- Spatula
- Petri dish for staining and de-staining
- Conical Flask 500ml
- Centrifuge machine
- Pipettes (1000 and 10 micro lt)
- 50ml beaker
- Bunsen Burner, Tripod Stand, Wire Mesh

Storage:

Alkaline Hemoglobin Electrophoresis Buffer can be stored in fridge for 1 week and used. But every time before using the buffer we should check the PH of the buffer- it should be 8.4.

Specimen Handling and Collection:

Collect whole blood in an anticoagulant tube (an EDTA tube is preferred) under sterile conditions (if to be used for future). Ensure that the blood sample is at room temperature before beginning the protocol.

Procedure:

I. Sample preparation

The quantity of sample required for the electrophoresis testing is 250 µl of blood, if patient's hemoglobin is less than 7 gm% then take 500 µl sample. For testing purposes red blood cells are to be separated from the fresh blood sample to isolate hemoglobin from them.

For doing that, Centrifuge the fresh whole blood sample at approximately 3000 rpm for 10 minutes at room temperature. Discard the supernatant plasma carefully such that the red blood cell pellet obtained, is not disturbed. Wash the red blood cell pellet with 2 ml of Normal Saline. Centrifuge the resuspended pellet at approximately 3000 rpm for 10 minutes. Again discard the supernatant carefully and wash the pellet with another 2ml of Normal Saline. Perform this wash step 5 times with Normal Saline to obtain a red blood cell pellet.

Discard the supernatant carefully at the end of the washing steps such that the red blood cell pellet remains undisturbed. Make sure that there is no normal saline remaining in the tube.

II. Lyse

a. Add 200-500 µl of Distil Water, mix the suspension well and let it stand for 10 minutes.
b. Add 200µl of CCL4 (Carbon Tetra Chloride), Mix well and centrifuge at approximately 3000rpm for 10 minutes.
c. Take the tubes carefully out of the centrifuge without disturbing the supernatant and pellet.

III. Preparation of Working Buffer

a. Mix 8 gm Tris buffer pre-weighed and 3.6 gm Glycine to 500ml of distilled water in a conical flask.
b. Check pH of the buffer, it should be 8.2 - 8.4.
c. This working buffer can be stored in fridge and reused 3-4 times, provided its pH is maintained at 8.4

IV. Agarose gel preparation

a. Prepare agarose gel by adding pre-weighed 320mg of Agarose in 40ml working buffer. Dissolve it completely by boiling in the working buffer.

NOTE: Prepare fresh diluted Gel Running Buffer as indicated in general preparation instructions NOTE: The agarose powder should be dissolved in diluted working buffer by boiling and swirling intermittently such that the agarose dissolves completely. Do not over boil the agarose so as to minimize water loss due to evaporation.

b. Cool the melted agarose for about 10 minutes, cover the open sides of the boat with cello tape. Pour the melted agarose while hot in the casting unit of electrophoresis unit with the two combs placed in their respective notches. Ensure that the gel poured spreads evenly on the surface of the casting tray to form a thin gel. Allow the gel to set. The gel will solidify completely in 15 minutes.

    NOTE: Do not pour the gel when it is boiling hot as it leads to water loss due to evaporation which will alter the concentration of agarose in the gel. The formation of a thin uniform gel is essential

to minimize resistance produced, which leads to generation of heat due to high voltage and high current required for the electrophoretic run.

c. Position the casting tray after the gel has set such that the wells are oriented towards the cathode.
d. Pour 450 ml of working buffer into the electrophoretic tank. Ensure that the agarose gel is submerged completely in the working buffer.
e. Load 5 µl of supernatant from each sample into each well.
f. Connect the electrodes of the Electrophoresis unit to Electrophoresis power supply unit and run the gel at 150 to 200 V and 90 mA for 1 hour. To ensure that the run has started the user can observe bubbles in the buffer from the sides of the electrophoresis unit.

Usually migration of protein band can be read after 1 hour without staining but if the bands are lightly colored and for clear reading we can go ahead with staining.

V. Staining of gel for visualization of hemoglobin protein bands

1. Slice the gel carefully along the edges of the casting tray using a spatula, such that gel can slide down easily into the staining tray. Avoid breakage of gel during handling.
2. Pour Amido Stain onto the gel such that the gel is completely submerged in the staining liquid. Allow staining by shaking the gel in the staining solution for 10 minutes.
3. Decant the stain used in a container. This stain can be reused 8-10 times. It should be stored in brown glass bottle.
4. Rinse the gel with 100 ml distilled water by pouring it in the tray and shaking the gel intermittently.
5. Decant tap water and pour 5% acetic acid into the tray for 30 minutes. Shake the gel intermittently.
6. Discard the acetic acid after 30 minutes.
7. Discard the acetic acid and take reading of the bands.

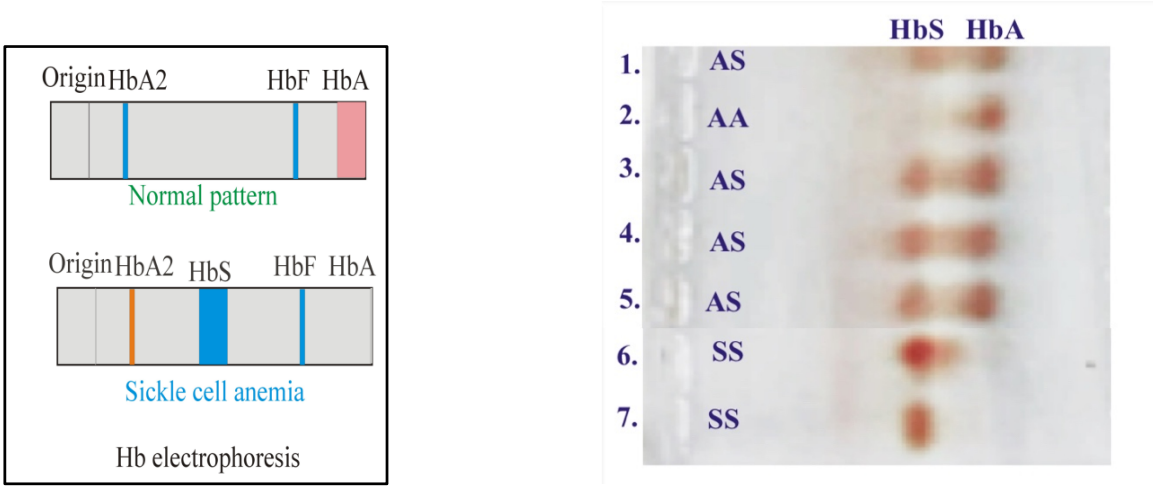


Fig - bands in the Hb Electrophoresis gel

5) HPLC (High Performance Liquid Chromatography) Interpretation:

HPLC gives exact percentage of each hemoglobin variant in blood. Normal adult composition of blood is as shown in table below. In sickle cell disease (SS) Hb S level is more than 85 % and in sickle cell trait HbS level is 35-45 %. More combinations of different hemoglobin types along with their diagnosis are mentioned in table below.

Caution: Sample for HPLC should be collected before blood transfusion or 4 months after previous transfusion so as to avoid false readings due to transfused blood.

Normal Adult Human Hemoglobin Composition

Hemoglobin	Structure	% of Normal Adult Hb
Hb A	$\alpha_2\beta_2$	>96%
Hb A2	$\alpha_2\delta_2$	~2.5%
Hb F	$\alpha_2\gamma_2$	<1%

Condition	Genotype	Older children (>= 5 years), adolescents, and adults				
		HbA (%)	HbA2 (%)	HbF (%)	HbS(%)	HbC(%)
Normal	AA	95 to 98	2 to 3	< 2	0	0
Beta Thalassemia Trait	A/β^0 or β^+	90 to 95	>3.5 (unless due to δβ: can be normal or lower)	1 to 3 (Significantly higher if due to δβ deletion)	0	0
Sickle Cell Trait	AS	50 to 60	< 3.5	< 2	35 to 45; may be lower if concomitant alpha thalassemia	0
Homozygous sickle Cell Disease (HbSS)	SS	HbA < HbS	< 3.5	5 to 15; may be higher in rare cases	HbA < HbS or HbS > 50%	0
Sickle β^0 thalassemia	Sβ^0	0	> 3.5	2 to 15	50+	0
Sickle – β^+ thalassemia	Sβ^+	5 to 30	> 3.5	2 to 10	50+	0
HbSC Disease	SC	0	< 3.5	1 to 5; may be higher in rare cases	45 to 50	45 to 50

Chapter - 3: Common Complaints in SCD

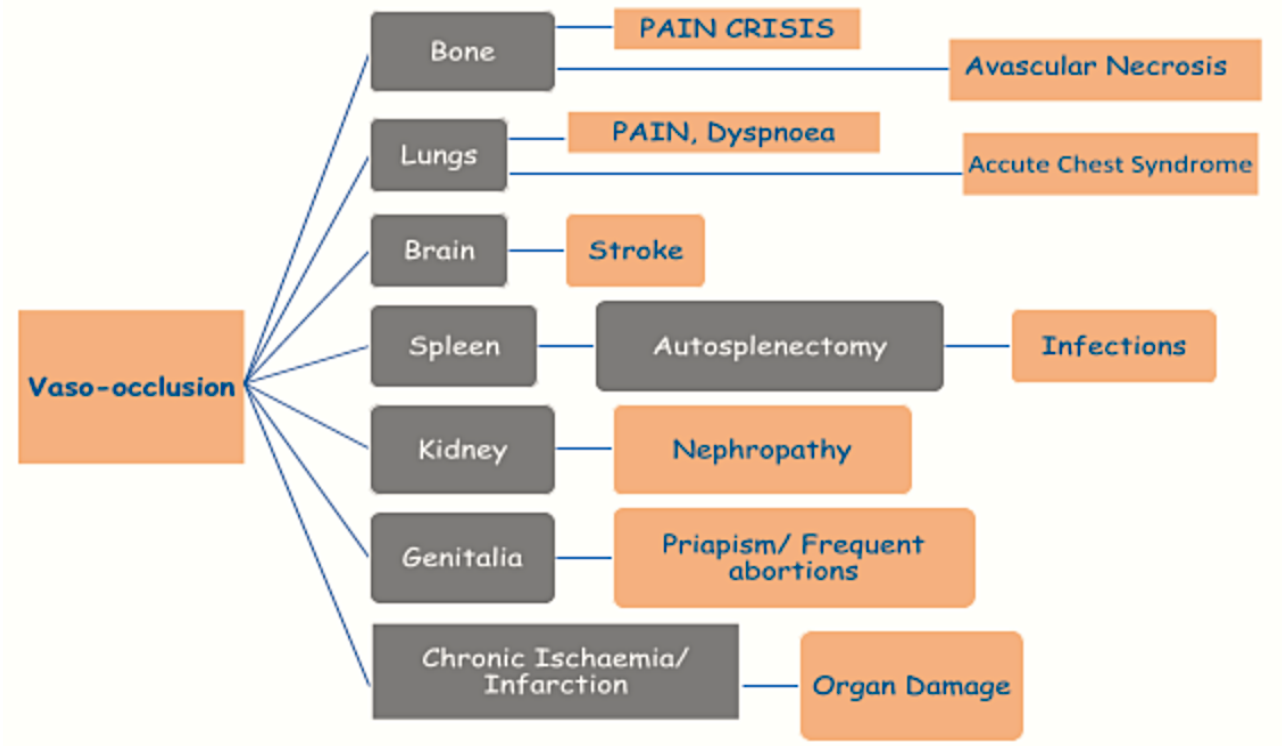
As discussed in the section- Pathophysiology, the common manifestation of the SCD are manifested based on two basic conditions i.e. Vaso-occlusion and Hemolysis.

1. Clinical Manifestation based on Vaso-occlusion:

Vaso-occlusion is mainly manifested as "PAIN". In analogy with Myocardial infarction (MI), one could say that there's multiple MI occurring in Bone, Lung, Spleen, Kidneys, Brain, in the order of frequency; thus, severe pain during Vaso-Occlusive crisis (VOC) is well explained.

When such Vaso-occlusion occurs in Spleen, infarction occurs in spleen leading to early auto splenectomy. Thus, making the patients prone to infections by capsulated organisms like Strep. Pneumoniae, Neisseria Meningitides, etc. Hence, SCD patients are immunocompromised and need frequent hospitalization for not only for PAIN but also for INFECTIONS.

The cycle of vaso-occlusion promotes future pain crisis, leading to tissue and organ damage, leading to chronic complications of SCD like Chronic pain, Pulmonary Hypertension, Avascular Necrosis, Leg ulcers, Retinopathy, Nephropathy, etc.



1. Clinical Manifestation based on Hemolysis:

- As sickled RBCs hemolysis frequently due to obstruction as well as due to deformed cell shape, it is manifested as Anemia and Jaundice. Anemia is manifested clinically as easy fatigability, breathlessness, requiring frequent blood transfusions.
- Jaundice is noted by yellowish discoloration of sclera. Also, due to frequent hemolysis, SCD patients are also at high risk for Cholelithiasis.
- When sudden pooling of the RBCs occur in spleen, leading to sudden drop in the Hb by 2 gm%; the condition is known as Splenic Sequestration Crisis. Massive splenomegaly is pathognomonic of this condition.
- Being an inherited disorder, history of similar complaints like pain, frequent jaundice, history of death in the family or siblings must be elicited in the case, to raise the suspicion for sickle cell disease.

FAQ 1: By what age, sickle cell disease is manifested? When can the very first manifestation of the SCD occur?

Pain crisis manifests when the level of HbS rises and HbF falls, usually by age 6 months. Actually the pathological levels of HbS starts appearing by 8 to 10 weeks of birth and potential life threatening complications might occur even at that age. But onset of significant clinical mortality may occur between 6 to 12 months of age. Also, such clinical manifestations may not occur in every patient of sickle cell disease. Clinical manifestations occur under the stressful stimuli, like dehydration, fever, infection, cold and hypoxia.

Common clinical manifestations of sickle cell disease in infancy are Dactylitis, acute chest syndrome and splenic sequestration crisis. Education and Prophylactic measures to prevent infections are important (like Penicillins and vaccine administration).

General Management of Sickle Cell Disease:

One must know that the process of sickling occurs under stressful conditions, which are precipitated by:

A. Cold
B. Infection
C. Dehydration
D. Hypoxia
E. Excessive exercise or manual labour
F. Women in labour

Even though we cannot treat the cause, being inherited disorder, the quality and span of life can be increased greatly by regular treatment and avoidance of precipitating factors.

Management:

1) Hydroxyurea:

Hydroxyurea aka Hydroxy carbide is the most important driver in managing SCD as of now. A Ribonucleotide Reductase Inhibitor mainly acts by increasing the HbF levels thus increasing the O2 carrying capacity and reducing the sickling episodes.

Other minor mechanisms of action are:

1. Decreases the number of Circulating WBCs and Reticulocytes as well as Adhesion molecules ⊠ reduction in Vaso-occlusion
2. Metabolism of Hydroxyurea - Releases Nitric Oxide- vasodilation of small and large blood vessels
3. Raises MCV
4. Reduces the cellular deformability and Rheology

Hydroxyurea is a chemotherapeutic agent for AML, ALL; but it was found to have increased levels of HbF, hence it was incorporated in the treatment of SCD.

Indications for starting Hydroxyurea in SCD:

1. Infants < 9 months, with symptomatic disease like dactylitis.
2. For Children: Age > 9 months onwards
3. In all adult patients with sickle cell disease as defined earlier:
   - > 3 sickle cell-associated moderate to severe pain crises/year
   - Sickle cell-associated pain - curtailing daily activities and affecting the quality of life
   - H/O severe & recurrent Acute Chest Syndrome.
   - severe symptomatic chronic anemia.

Contraindication of Hydroxyurea:

1. Pregnancy
   - It is preferable to hold Hydroxyurea in pre-conceptional period (3 months before planning of conception) for both men OR women with SCD. Weaning can be started at 6 month postpartum and Hydroxyurea resumed thereafter.
   - Pregnancy and breastfeeding — Hydroxyurea is considered to be an embryonic and fetal toxin based on animal studies, and it should not be used during pregnancy. However, evidence of human teratogenicity is lacking. Hydroxyurea is excreted in breast milk. Our approach to preconception planning, pregnancy, and postpartum use is as follows:
   - Females of reproductive potential who are receiving hydroxyurea should be counselled to use effective contraception. For those who wish to become pregnant, it is prudent to discontinue hydroxyurea three months before conception. Other aspects of pre-pregnancy planning are discussed in detail separately.
   - Males of reproductive potential who are receiving hydroxyurea should be advised to use effective contraception. For those who wish to have a child, it is prudent to discontinue hydroxyurea six months before conception.
   - If a patient becomes pregnant while taking hydroxyurea, we discontinue the drug immediately. Most outcomes of pregnancies conceived while taking hydroxyurea are good, although there are few data that address this issue. Clinical and hematologic monitoring upon discontinuation of the drug is important, since the patient may experience a worsening of symptoms (eg, pain crises) once the drug is stopped. We restart hydroxyurea once the infant is no longer breastfeeding. Transfusion during pregnancy is discussed separately. The duration of breastfeeding is based on balancing the benefits to the infant and mother against the risks associated with not taking hydroxyurea for that individual.
2. WBCs < 2000
3. Absolute Neutrophil Count < 1500
4. Platelets < 80,000

Barring the above contraindications when can we avoid giving Hydroxyurea to patients with SCD.

Dosages of Hydroxyurea:

- Dose: 10 - 35 mg/kg
- Start the dose at 15 – 20 mg/kg then increase by 5 mg/kg every 2 months depending upon the response.
- It is given as once a day (OD dose).

Weight-based chart for starting Hydroxyurea:

Weight Range (Kg)	Dose (mg)	Quantity of drug to be taken(for 500 mg Cap)
5 to 7.5	125	¼ Capsule (OD)
7.6 to 12.5	180	1/3 Capsule (OD)
12.6 to 17.5	250	½ Capsule OD or 1 Cap alternate day (OD)
17.6 to 22.5	300	½ capsule (OD)
22.6 to 27.5	375	1 Cap on the odd day & ½ Cap on even day (OD)
27.5 to 32.5	450	1 Cap (OD)
32.6 to 37.5	525	1 Cap (OD)
37.6 to 42.5	600	1+ 1/3 Cap (OD)
42.6 to 47.5	675	1 ½ Cap (OD)
47.6 & onwards	750	1 cap on an odd day & 2 caps on an even day (OD)

Precaution and Monitoring while on Hydroxyurea:

Following points should be checked

1. Clinical criterion like_ Frequency of Pain crisis; of blood transfusion; Anemia

If there is no clinical improvement in the period of 2 months after starting Hydroxyurea, the dose needs to be increased by 5 mg per 2 monthly while testing for the blood investigations. If there's an improvement in the symptoms one must continue that dose lifelong.

2. WBCs count (2 monthly)
    a. WBC count <2000
    b. Absolute Neutrophil count. If the absolute neutrophil count falls below 1500
    c. Platelets: If platelet counts fall below 80,000
    One must stop Hydroxyurea therapy for short period of time ie. 2 weeks. And then restart the therapy at original dose if the counts have returned to normal
3. Serum Creatinine levels at least 6 monthly
    Reduce the dose of Hydroxyurea by half if the Creatinine Clearance is <60ml/min.
4. Liver Function Test every 6 monthly. SGPT

FAQ 2: Will the Hydroxyurea cure the SCD?
No, Hydroxyurea can-not cure the SCD but it keeps the disease controlled. Gene therapy and bone marrow transplantations are the only cure for the disease. But these treatments are very costly.

2) Hydration:

- One is asked to drink a lot of water per orally; so much so that one should be able to pass urine at least 3 hourly during the day.
- When Sickle Nephropathy occurs, it may be required to decrease water intake.
- Hydration is a necessary step for controlling pain crisis as well.

3) Folic Acid:

SCD is a type of Hemolytic anaemia where Iron deficiency is not usually expected. Hence Iron should be avoided unless required. Being a membrane defect and increased Red cell turnover, one must provide Folic Acid at a dose of 2.5 mg per day.

1. Folic Acid
   → 2.5 mg per day OR 5 mg Alternate day.
2. Iron Supplement
   → Only if iron deficiency noted
   - MCV Low (<65/fL) & Response to iron therapy is noted in 1 month

4) Blood Transfusion:

Criteria for blood transfusion are

1. For asymptomatic patients Hb < 5.5 gm/dl in children or <6 gm/dl in adults
2. Associated complications
   a. Acute Chest Syndrome
   b. Splenic Sequestration Crisis
   c. Aplastic Crisis
   d. Stroke
   e. Fever
3. Peri-surgical period
4. Pregnancy

(for 2,3,4 above, target Hb after transfusion is 10 gm/dl)

Packed Red blood cells are preferred than whole blood. But in case of non-availability of packed cells whole blood is acceptable. One must avoid blood transfusion if Hb is more than 10gm%; in view of Hyperviscosity and hemoconcentration leading to higher chances of Vaso Occlusive Crisis.

5) Prevention of Infection:

As patients are at high risk of infection due to auto splenectomy in SCD, following prophylaxis therapy and immunization is must

1. Antibiotic Prophylaxis:
   → Oral Penicillin: For all children below 5 years of age with Sickle cell disease in the following dose
   - 125 mg BD for age below 3 years
   - 250 mg BD for age more than or equal to 3 years

   → If Oral Penicillin is not available, then one could use Amoxicillin tablets in above mentioned dose.

2. Immunization: Complete childhood immunization should be done including pentavalent and PCV13 as prescribed in months 2 ,4 and 6.

- Pneumococcal (PCV13) vaccine—
  NOTE: Children who have not received the above immunization schedule must receive one dose of PCV13 after infancy.
- Pneumococcal vaccine-naïve Adults and children over 5 yrs :-
  Should receive
    a. One dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later.
    b. A second PPSV23 dose is recommended 5 years after the first PPSV23 dose.

3. Hib: - One dose of Hib vaccine for people aged >5 years who have SCD if they have not previously received Hib vaccine

FAQ 3: How long can patients with sickle cell disease live?
Answer: if the patient continuously get appropriate treatment then patients can live a normal life.

Chapter - 4: Complications in Sickle Cell Disease

The clinical manifestations of sickle cell anemia affect all organ systems and are mainly due to two mechanisms- hemolysis and reduced blood flow due to vaso - occlusion. Hemolysis results in a reduced RBC life span of around 17 days as against a normal life span of 120 days. This results in anemia, jaundice and features of extramedullary and medullary hematopoiesis. Vaso-occlusion leads to tissue ischemia and infarction which leads to complications like acute and chronic pain, bone infarcts, avascular necrosis, acute chest syndrome, cortical infarcts, renal papillary necrosis, splenic infarcts leading to hyposplenism, placental infarcts etc.

1. Vaso-occlusive Pain-

- This is the commonest reason for seeking care in patients with sickle cell disease. Pain may be acute or chronic.
- Acute pain is caused by vaso-occlusion, ischemia, inflammation.
- Chronic pain arises due to complications such as compression fractures, AVN, arthropathies, leg ulcers, etc.
- Pain should be assessed rapidly with respect to location, duration and severity. Since no test exists to confirm whether a patient is in pain, the gold standard for assessment of pain is the patient's self- reported assessment which should always be believed.
- Associated conditions like acute chest syndrome, bone infarction, stroke, splenic sequestration etc. should be looked for.

Initial Home management consists of the following-

- Mild pain-PCM, NSAIDS
- Moderate pain- opioids (Codeine, Tramadol)
- Severe pain- Admit
- Treat with morphine, pentazocine, fentanyl as described in the section on pain.
- Look for associated fever, cough, tachypnea, symptomatic anemia, sequestration, stroke
- Hydration with one and a half times maintenance I/V fluids*
- Blood Transfusion, Oxygen should be given only if indicated.
- Venous Thrombo-embolism prophylaxis should be given in adults.
- Psychosocial support, distraction, relaxation exercises are other supportive therapies which should be used.

HYDROXYUREA-

- Reduces frequency and intensity of pain episodes by almost 50%
- Treat chronic pain with hydroxyurea, opioids and NSAIDS
- Prevention includes adequate hydration and rest and avoiding cold and strenuous activity.

*Calculation of the hourly maintenance fluid rate for a child who weighs 25kg. (4ml x 10kg) + (2ml x 10kg) + (1ml x 5kg)
= hourly rate. 40ml + 20ml + 5ml = 65ml/hr.

2. Fever in SCD

Fever in sickle cell disease is the first indication of life-threatening infection. It is also a feature of associated conditions such as acute chest syndrome or vaso- occlusive pain episodes. In children with sickle cell disease, fever is the commonest cause of death. Auto infarction leads to functional asplenia which predisposes these patients to the risk of invasive bacteremia.

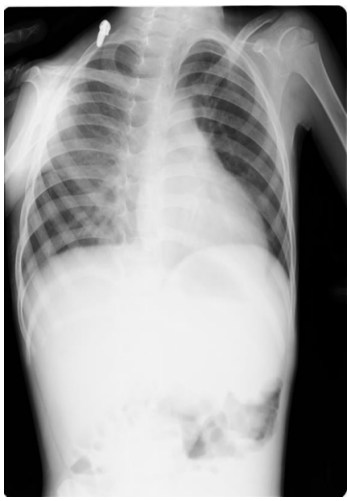
Since fever may be the first and only sign of a serious infection, patients should be counselled to seek care for any temperature greater than 101.5*F(38.5*C). They should be evaluated ideally within 4 hours of the onset of fever. Providing them with a thermometer and teaching its use is an important step.

A brief history and examination should be carried out to localize the site of infection, hemodynamic instability, any associated complications such as vaso-occlusive pain crisis, acute chest syndrome, splenic sequestration crisis, osteomyelitis etc should be looked for.

Lab tests including a CBC with a total and differential leukocyte count and reticulocyte count should be carried out Blood culture should be done if available. A peripheral smear for malaria parasite should be done.

- Chest x-Ray in presence of respiratory signs
- Urine examination in a child less than 2 years or if signs of a UTI are present, CSF examination in the presence of signs of meningitis should be done.
- Empiric parenteral antibiotics should be administered within an hour of the patient being evaluated
- I/V Ceftriaxone is the preferred antibiotic in a dose of 50-75 mg/kg, 100 mg/kg in meningitis
- Criteria for admission include:
    - age less than 2yrs.,
    - Temp.> 104*F,
    - TLC> 30,000 or <5000,
    - Hb fall >2gm from baseline,
    - fever that is associated with moderate to severe pain,
    - previous history of invasive infection or any associated complications
- Occasionally If the above are absent and the patient looks well, is clinically stable, lives nearby and can come back for follow up the next day, the patient may be discharged and follow up on an out-patient basis.

Case Name: Bharti Baiga, 7 years old girl



Complaints:

- H/O Fever, cough, pain in the legs for 4 days,
- H/O recurrent episodes of pain in the limbs, chest, abdomen for 1 year,
- H/O Jaundice 1 year back, no BT,
- 1 sibling death at 3 month of age
- O/E: Temperature 104 degree F, Chest-crepts B/L, Hepatomegaly

Investigations:

- Hb - 6.4 gm/dl, TLC - 10,400, DLC - P70 L30
- MP - Negative
- PS - fixed Sickle Cells, Sickling Test - Positive
- Hb Electrophoresis report - SS

Rx :

- I/V Ceftriaxone
- Azithromycin
- Paracetamol
- Blood Transfusion

Prevention of Infection:

Prevention of infection is an important part of management and includes the following-

- Immunization- routine childhood immunization including HIB, pneumococcal vaccines
- Prophylactic penicillin up to at least 5 years of age

Early assessment and management of fever with empiric parenteral antibiotics.

3. Acute Chest syndrome

ACS is the second most common cause of hospitalization (after vaso-occlusive pain) and the commonest cause of death in patients with sickle cell disease. Etiology may be multifactorial. In children infection and vaso-occlusive pain are the most common identified causes.

- In 50%, it develops during hospitalization for another cause like voc, post operatively, post-partum, etc.
- Peak incidence in children 2-4 yrs.
- Risk factors- asthma, smoke exposure, chronic hypoxemia

Diagnosis is based on the presence of the following-

- New infiltrate on CxR with one or more of the following:
- Chest pain.
- Temp. > 38.5^0 C
- Hypoxemia
- Tachypnea, wheezing, cough
- Increased work of breathing

Management:

- Treat infection- Ceftriaxone + Azithromycin
- Analgesia, maintenance fluids
- Resp. support to maintain SpO2> 92%, O2, CPAP, NIV, Mech. Ventilation
- Bronchodilators and steroids for asthma
- Early transfusion to bring Hb to 11g/dl as this helps in improving oxygenation and reduces sickling in the pulmonary vascular bed.
- Exchange transfusion is indicated in severe disease which progresses despite treatment.
- Prevent recurrence of ACS

⇒ Prevent infection by immunization and use of prophylactic antibiotics.
⇒ Treat asthma
⇒ HYDROXYUREA reduces the risk of acute chest syndrome by 40% in adults and 3-fold in children
⇒ Prophylactic transfusions can also be used in those who have recurrent ACS despite being on hydroxyurea.

4. Other Pulmonary Complications

- Chronic dyspnea
- Restrictive lung disease
- Pulmonary fibrosis
- Asthma
- Sleep-disordered breathing

5. Pulmonary hypertension

Fact: Pulmonary hypertension occurs in 6-11 % of patients with sickle cell disease.

It is a risk factor for mortality. Symptoms include dyspnea on exertion, fatigue, palpitations, chest pain, edema and syncope. Pulmonary hypertension in sickle cell disease results from endothelial injury due to recurrent hemolysis, acute and chronic inflammation, chronic intravascular hemolysis, hypercoagulability and reduced bioavailability of nitric oxide.

Diagnosis of Pulmonary HT

- SpO2 < 94% at rest or drop of > 4% on activity
- Physical examination reveals features similar to those seen in patients with pulmonary hypertension without SCD such as loud P2, parasternal heave, murmur of tricuspid regurgitation and features of right heart failure such as hepatomegaly, ascites, edema etc.
- CxR may show a prominent pulmonary artery segment. ECG shows p pulmonale in lead 2.
- Echocardiography shows a Tricuspid regurgitation velocity > 2.5 m/sec, and increased pulmonary artery and RV systolic pressures.
- 6 min walk test to assess the distance walked and desaturation with exertion is also indicative
- Confirmation of the diagnosis is done with Right heart catheterization

Treatment of Pulmonary HT

- Supportive treatment includes O2 supplementation to maintain an SpO2> 90%
- Treatment of associated conditions such as obstructive sleep apnea,asthma, nocturnal hypoxemia
- HYDROXYUREA should be started if the patient is not receiving it already.
- Chronic transfusion consisting of monthly transfusions can be given to those patients who do not improve with hydroxyurea.
- Pulmonary Vasodilators- Endothelin receptor antagonists, prostanoids. Sildenafil and calcium channel blockers are not recommended. Careful diuretic therapy to minimize the risk of volume depletion induced sickling can be used to treat right ventricular volume overload.
- Long term Anticoagulation is used if there is underlying venous thromboembolism and no bleeding risk.

6. Stroke

Stroke is a common complication of sickle cell disease and both ischemic and haemorrhagic stroke can occur. It is estimated that without treatment 11% of patients with sickle cell disease will have a stroke by 20 years of age and 25% by 45 years. Any patient with sickle cell disease who presents with severe headache, neurological deficit or altered sensorium should be evaluated for stroke after excluding conditions like acute meningitis, cerebral malaria, todd's paresis etc.

Diagnosis:

MRI if available is preferable over a CT scan for diagnosis and differentiating between acute ischemic and hemorrhagic stroke. A complete CBC and blood grouping and cross matching should also be done.

Treatment:

An acute ischemic stroke should be treated by exchange transfusion to reduce the percentage of sickled RBC's to less than 30% while maintaining a hemoglobin level of 10 gm/dl. A simple transfusion may be given while one is arranging for an exchange transfusion or before transferring the patient to a facility where an exchange transfusion can be carried out. Aspirin therapy is used in ischemic stroke. However, thrombolytic therapy is not used in patients with sickle cell disease and acute ischemic stroke. Anticoagulation therapy may be given prophylactically to adults with sickle cell disease admitted with a medical problem.
A patient with sickle cell disease and stroke should be started on chronic transfusion therapy and HYDROXYUREA to prevent a recurrence.

Primary prevention:
Measurement of trans cranial Doppler velocity is carried out in children between the ages of 2 to 16 years followed by chronic transfusion therapy in children at risk. Patients should be screened and treated for hypertension to prevent hemorrhagic stroke. Any child presenting with unexplained cognitive decline, developmental delay or focal deficit "should be screened for silent stroke.
NOTE: Other neurological complications in sickle cell disease include TIA, seizures, PRES

7. Anemia

Sickle cell disease is characterized by a chronic compensated hemolytic anemia.
Lab findings reveal a hemoglobin of 8-10 g/dl, mild leukocytosis and reticulocytosis. The anemia may be normocytic, normochromic, or mild macrocytic or microcytic if associated thalassemia or iron deficiency is present.

Acute exacerbations of anemia may be caused by-

- Aplastic crisis
- Splenic or hepatic sequestration crisis

8. Aplastic Crises

These occur due to infections such as Parvovirus B19, Pneumococcus, Salmonella, EBV etc. They are characterized by -

- Fall in Hb by >2 g/dL from the steady state
- Low Hb, low Retics < 1%
- The aplasia is transient and usually recovers in 2-14 days.
- Treatment is with blood transfusions until spontaneous recovery occurs.

Splenic or hepatic sequestration-

- This occurs due to pooling of a large quantity of blood in an organ (spleen, liver)
- Infants and children are affected more commonly with splenic sequestration.

Clinical features-

Sudden pooling of a large volume of blood gives rise to

- Tender splenomegaly or hepatomegaly
- Hypovolemic shock may lead to death even before the child reaches the hospital. It is associated with a mortality of 10- 15 %.
- Anemia, thrombocytopenia, reticulocytotic

- Treat with fluids and blood transfusion
- 50% chance of recurrence- prevent recurrence by teaching spleen self-palpation so that the parents can recognize the complication and seek early medical care. Splenectomy is indicated in case of recurrence.

9. Skeletal Complications

The commonest skeletal complication is vaso-occlusive pain crisis which is the commonest cause for admission in a patient with sickle cell disease. Pain episodes lead to bone infarcts, necrosis and degenerative changes over time in marrow containing bone.

9.1 Dactylitis –

This is the occurrence of vaso-occlusive pain in the small bones of the hand in children between 6 months to 4 years of age. Dactylitis is not seen in older children as the red marrow in these bones is replaced by fat and fibrous tissue. Dactylis presents with painful, symmetrical swelling of the hands and feet associated with erythema and mild fever. X-ray shows soft tissue swelling. Differential diagnosis includes osteomyelitis which usually affects only a single-digit or bone. Treatment consists of hydration, analgesics, anti-inflammatory drugs, warm packs and HYDROXYUREA which plays a significant role in preventing this complication.

9.2 Osteomyelitis and Septic Arthritis

Infection in areas of infarcted bone due to splenic hypofunction leads to this complication. Osteomyelitis is much more common than septic arthritis. Symptoms include prolonged fever and pain along with swelling at a single site which differentiates it from a vaso-occlusive pain crisis.

Diagnosis-

X-ray changes appear at 7-10 days and thus not useful in pain less than 7 days. Biopsy and aspiration of suspected focus(gram stain of aspirate) should be carried out to isolate the organism and confirm the diagnosis where possible. Common organisms causing osteomyelitis in patients with sickle cell disease include Salmonella, E.coli and Staph. aureus.

Treatment-

Treatment is with antibiotics (ceftriaxone and ampiclox) which cover these organisms and drainage. Antibiotics should be given for an adequate duration-2 weeks I/V followed by 2 to 4 weeks of oral antibiotics if osteomyelitis is confirmed.

9.3 Avascular Necrosis (AVN)

This is a common complication of sickle cell disease and occurs due to infarction of bone trabeculae. It may affect both the femoral and humeral heads.

AVN of the femoral head is more common and is characterized by the following features-

- 10% of SCD patients affected, prevalence increases with age
- Femoral head undergoes progressive destruction due to chronic weight-bearing
- Reduced mobility, gait abnormalities, limb length discrepancies, B/L involvement is common.

AVN of the humeral head is seen in 5-6% of patients with sickle cell disease.

Management:

- Early – Conservative Management
- Analgesia, rest, reduced wt. bearing, physiotherapy
- Core decompression if no relief with conservative Rx
- Arthroplasty is associated with a high failure rate with serious peri-operative & postoperative complications. Hence it should be considered only if conservative management fails and there is severe joint involvement.
- Early detection is important to delay progression
- High HbF is protective- hence HYDROXYUREA plays an important role in prevention.

10. Hepatobiliary complications

The liver in sickle cell disease can be affected by several complications due to the disease itself as well as its treatment. These include-

- Acute ischemia
- Cholestasis
- Hepatic sequestration
- Cholelithiasis
- Iron overload
- Viral hepatitis

Cholelithiasis results due to the increased rate of hemolysis which give rise to pigmentary gallstones. Symptomatic gallstones should be managed surgically. Laparoscopic cholecystectomy is preferable to open cholecystectomy as postoperative complications are lesser. However, the complications due to sickle cell disease are the same with both procedures. Preoperative blood transfusions should be given if Hb is less than 9 to reduce the occurrence of postoperative acute chest syndrome and vaso-occlusive pain crisis.

11. Renal Complications

Several renal manifestations occur in patients with sickle cell disease. These include -

- Defect in urinary concentrating ability manifesting as enuresis at around 10 years of age
- Hematuria due to papillary infarcts, more rarely due to renal medullary carcinoma
- Proteinuria leading to progressive renal disease
- Hypertension
- FSGS leading to ESRD
- Nephrogenic Diabetes Insipidus

Management:

Screening for kidney disease should be carried out every 4-6 months in all children above 5 years of age and every 2-3 months in adults. Screening consists of measurement of serum creatinine, urine microscopy, urine protein creatinine ratio, and urine dipstick for hematuria. An ultrasound may be carried out if hematuria is present. A CT scan of the abdomen may be needed in the presence of hematuria to rule out a renal medullary carcinoma.

ACE inhibitors should be given in the presence of proteinuria.

Hypertension should be treated if present. Diuretics should not be used as they may cause volume depletion.

12. Leg Ulcers

- Painful ulcers due to vaso-occlusion in the skin.
- It presents after 10 yrs. of age, males more commonly affected.
- Spontaneous or after trauma,
- Medial and lateral malleolus, B/L.

Prevention-

- Well-fitting shoes,
- aggressive Rx of skin injury
- Antibiotics,
- local wound care,
- debridement,
- blood transfusion,
- hydroxyurea

13. Retinopathy

Sickle cell disease can cause a proliferative retinopathy due to retinal artery occlusion and ischemia followed by neovascularization along with virial hemorrhage and retinal detachment. Reduced visual acuity occurs though blindness is uncommon.

Annual ophthalmologic examination starting at 10 yrs. of age and continuing annually should be carried out and include visual assessment, visual field charting and a fundoscopy.

Treatment is by laser photocoagulation.

14. Priapism

Penile erection in the absence of sexual activity or desire is a common complication of sickle cell disease. Repeated untreated episodes may result in penile dysfunction.

Priapism may be ischemic or non-ischemic. It is precipitated by dehydration, drugs or sexual activity. The episodes may be recurrent lasting for less than 4 hours- called stuttering priapism or they may last for more than 4 hours known as major priapism.

Treatment:

- Stuttering priapism should be treated with analgesics and hydration. Patients should seek medical attention for episodes which last for more than 4 hours.
- They should be admitted for analgesia, hydration and urgent urologic evaluation. For episodes which do not respond to conservative measures, aspiration of corpus cavernosum with or without saline irrigation followed by injection of alpha-adrenergic agonist should be carried out.
- If this does not help then a surgical shunt should be carried out.
- Subsequent episodes can be reduced by the use of hydroxyurea or repeated blood transfusions if hydroxyurea is not effective.

15. Thromboembolism prophylaxis

Patients with sickle cell disease have a hypercoagulable state at baseline in addition to risk factors that increase the risk of thromboembolism such as infection and immobility. All adults admitted to the hospital with an acute medical condition such as acute chest syndrome, pain crisis, pneumonia or other febrile illness, pregnancy and delivery should be given thromboembolism prophylaxis with 5000 units of subcutaneous heparin thrice a day.

Chapter - 5: Pain management in Sickle Cell Disease

Pain is the most common reason to seek care for patients with Sickle Cell Disease. It requires rapid assessment and management, Check vitals- offer oxygen if SpO2 < 95%.

It is important to rule out more serious complications of Sickle cell disease (SCD) which needs separate evaluation and treatments besides analgesia; however, the initial assessment should not delay pain treatment.

Vaso-Occlusive Pain: Can be severe, unpredictable

Possible triggers-
- Dehydration,
- Infection,
- Cold temperature,
- Over-exertion,
- Hormonal changes (onset of menses),
- Exposure to tobacco/air pollution etc.
- Sometimes, no precipitating cause.

Common locations-
- upper back,
- either arm,
- legs,
- chest,
- abdomen,
- lower back

Assess intensity-

Believe the patient when he/she reports pain. No objective / subjective test can rule out its presence.

Avoid negative attitudes towards patients as it may hinder the successful treatment of pain.

Wong - Baker Faces Pain Rating Scale for Children / Visual analog for Adults

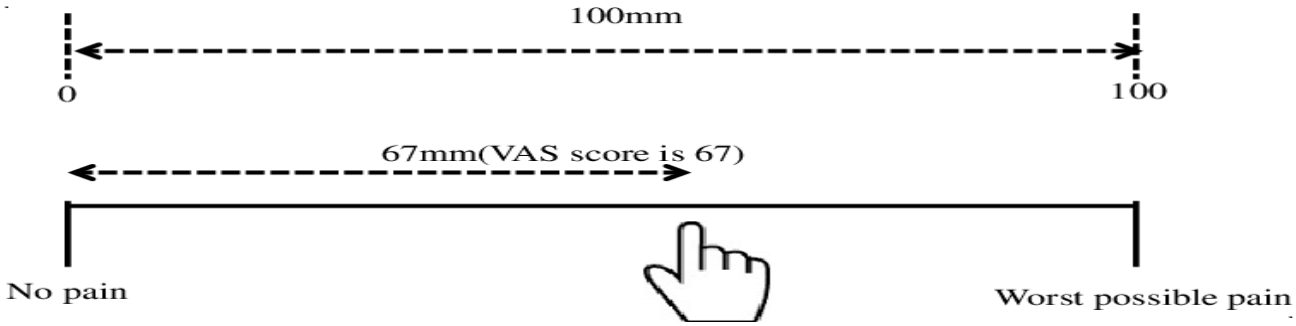
Instructions for Usage

Explain to the person that each face represents a person who has no pain (hurt), or some, or a lot of pain Face 0 doesn't hurt at all. Face 2 hurts just little bit. Face 4 hurts a little bit more. Face 6 hurts even more. Face 8 hurts a lot. Face 10 hurts as much as you can imagine. Although you don't have to be crying to have this worst pain. Ask the person to choose the face that best depics the pain they are experencing.

Interpretation of wong Baker scale

0 - 2 : Mild Pain ; 4 - 6 : Moderate pain ; 8 - 10 : severe pain

VISUAL ANALOG SCALE (VAS)



0-4 mm: No Pain 5-44 mm: Mild Pain 45-74 mm: Moderate Pain 75-100 mm: Severe Pain

Duration - can last hours to days, some patients have chronic pain (never pain-free)

Pain Management:

Mild Pain -
- NSAIDS or
- Paracetamol

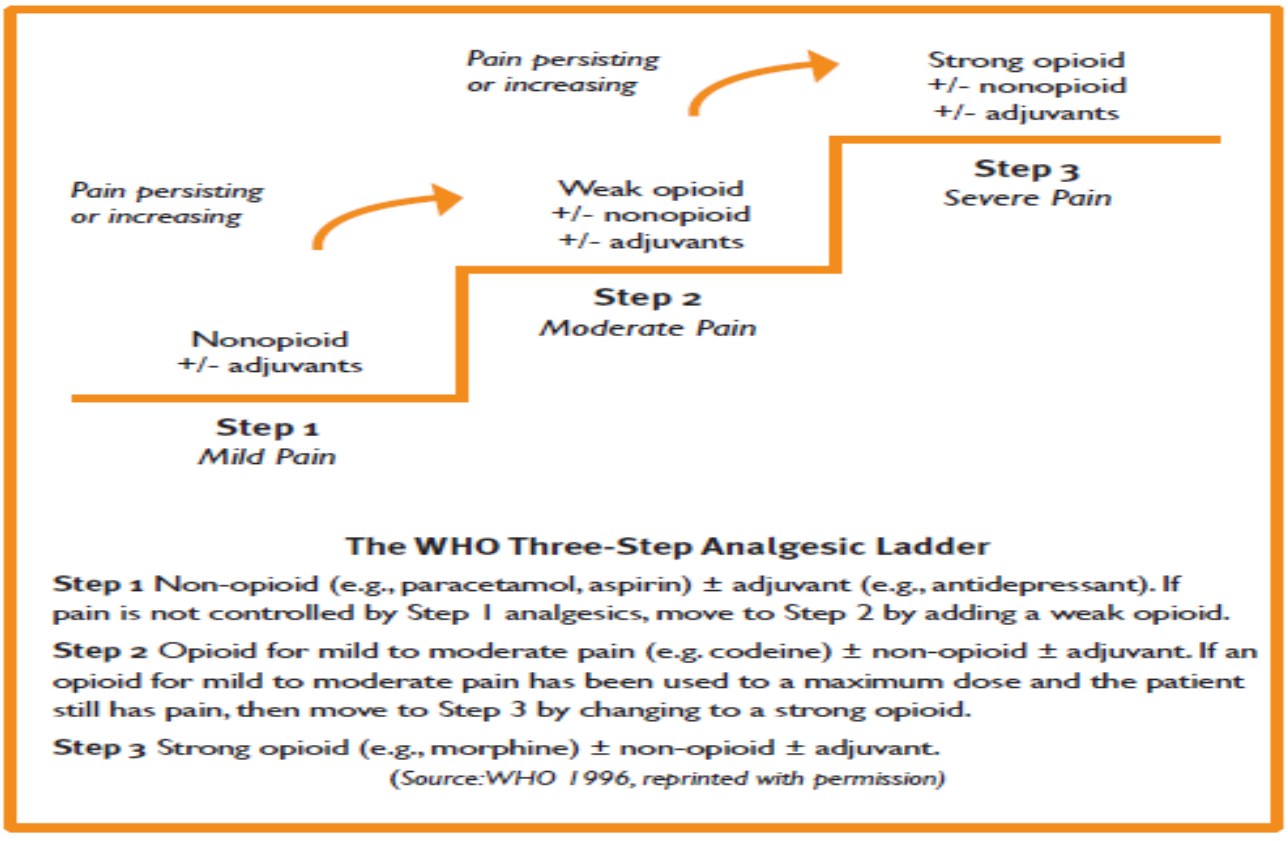
Moderate Pain -
1. NSAIDs and/or
2. Opioids:
- Codeine/tramadol

NOTE: Mild and moderate pain can be managed at home.

Severe Pain -
Admit, offer analgesia within 30 min. of presentation
- Will need strong opioid- i.v. morphine or fentanyl and NSAIDS/paracetamol
- Reassess in 20-30 min. and at-least every 4 hrs thereafter
- Manage opioid-related side effects- pruritus, vomiting, constipation, sedation
- Once pain relieved, offer long-acting oral/i.v. analgesic

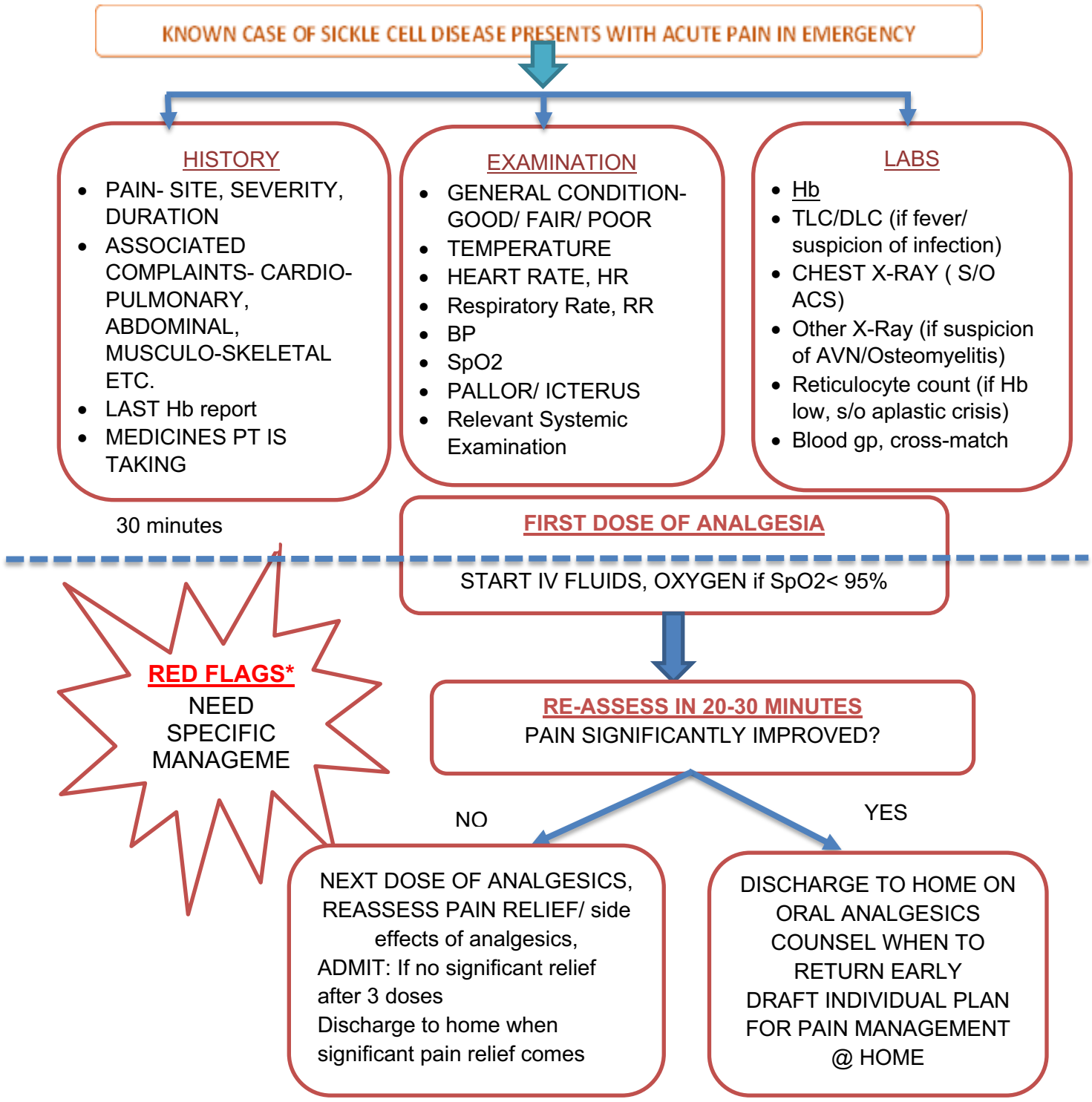
W.H.O. APPROACH TO PAIN MANAGEMENT

The WHO devised an analgesic ladder which provides a framework for the pharmacological management of pain.



- Start patients on Step 1 analgesics for mild pain; if these are ineffective, change to a Step 2 analgesic, then to Step 3 as required.
- If Step 1 or 2 analgesics don't work, don't switch to another analgesic at the same level: move up a step.
- The choice of analgesic depends on the severity, site and type of pain.
  - By the mouth/appropriate route: use the oral route whenever possible.
  - By the clock: administer analgesics according to a regular schedule rather than according to an as-needed schedule.

- The interval is determined by the pharmacokinetics of each medicine.
- By the ladder: use the WHO analgesic ladder. If after giving the optimum dose, an analgesic does not control pain, move up the ladder; do not move sideways in the same efficacy group.
- Individualized treatment: the right dose is the one that relieves the pain. Titrate the dose upwards until pain is relieved or undesirable effects prevent further escalation. Check to see that patient and carriers understand.
- Use of adjuvant drugs alongside analgesics



***RED FLAGS**: TEMP <36˚C or >38˚C, HR>90/min, RR> 20/min, SHORTNESS OF BREATH/COUGH/CXR INFILTRATES, PREGNANCY, HEADACHE/CONFUSION/SEIZURES, ACUTE SWOLLEN JOINTS, PRIAPISM, SEVERE ABDOMINAL PAIN/VOMITING/JAUNDICE.

Common Pain Medicines:

Drug	Dosing from	Adult dose	Pediatric dose	Safety profile
Paracetamol	1. Tablets, 2. Oral Suspension, 3. Infusion I.V., 4. Suppositories	325-650 mg /4-6h; 1 g/8h	10 mg/kg every 4 hours; 15 mg/kg every 6 hours	Hepatotoxicity, Renal toxicity
ibuprofen	1. Tablets, 2. Oral suspension	400-600 mg/ 6-8 h	20 mg/kg/day in 3-4 divided doses	G.i. irritation, G.i. ulceration, Platelet inhibition, Renal failure
Diclofenac	1. Tablets, 2. suppositories, 3. injection	50 mg/ 8h PO 75 mg/24 h im	Not Recommended	
Naproxen	1. Tablets	250-500 mg per 12 hours	10 mg/ kg/day in 2 divided doses	
Tramadol	1. Tablets, 2. injection	50-100 mg/4-6h PO/ i.v. over 3 min.	Not Recommended	Increased risk of serotonin syndrome, Lowers seizure threshold, vomiting, sedation
Fentanyl	1. Injection	1-2 ug/kg	1-2 ug/kg	Respiratory depression
Fortwin (Pentazocine)	1. Injection	30 mg slow i/v or i/m	0.5 mg/kg i/v slow q 6 hourly	Nausea
Morphine	1. Tablets, 2. injection	10-30 mg/3-4h PO 5-10 mg i.v./s.c.	0.3 mg/kg every 3-4 hour PO 0.1-0.15 mg/kg every 2-4h	Avoid in renal dysfunction, Constipation, Pruritus, Vomiting, Sedation

FAQ 1: Is drug addiction a real risk while offering narcotic analgesics to a patient presenting with repeated episodes of severe pain?

Sickle Cell Disease patients present frequently in an emergency with severe pain. Often they know which drug relieves their pain. This specific behavior of a patient asking for a specific drug (especially opioids - like morphine etc.) is seen by doctors/nurses as a drug-seeking behavior or development of addiction. This is a myth. If drugs are given at required doses with proper monitoring and follow-ups, there is a little real risk of addiction. Due to unreasonable fear in the medical professional, appropriate drugs should NOT be withheld.

HYDRATION- oral or i/v.; maintain urine output > 0.5ml/kg/hr

Adjuvants - depending on the type of pain e.g.

- antidepressants such as amitriptyline (for neuropathic pain)
- anticonvulsants such as carbamazepine, sodium valproate, and gabapentin (for neuropathic pain)
- antispasmodics like hyoscine (for abdominal or renal colic)
- anxiolytics/muscle relaxants like diazepam (for anxiety-related pain)

Non-pharmacologic measures (distraction, relaxation techniques, Cognitive behavioural therapy, local heat application, massage etc.)
On discharge, counsel on prevention of triggers, to regularly take hydroxyurea if indicated, design a treatment plan for acute pain to equip them to manage their pain at home when to seek care early- this improves patient satisfaction, reduces the need for hospitalization.

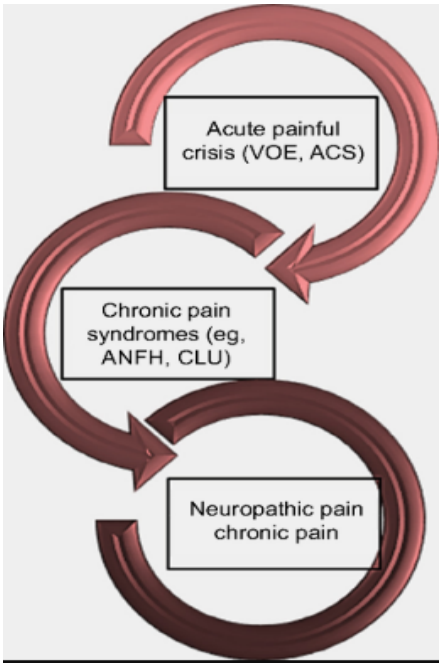
Pain syndromes in Sickle Cell Disease

(VOE-vaso-occlusive events, ACS- acute chest syndrome, ANFH-avascular necrosis of femoral head, CLU-chronic leg ulcers)

Chronic Pain

- Associated with avascular necrosis of the femoral head, neuropathic pain, or pain related to persistent low-grade inflammation involving the chest, back, upper and lower extremities, and rarely leg ulcers.
- Chronic pain often is associated with neuropathic pain, which is caused by nerve damage. It often is described as tingling, burning, numbing, or lancinating (sharp) and may be described as a sensation of pins and needles.
- The approach needs to be multi-disciplinary. May need a referral to a higher centre.
- Long-acting/ round the clock oral opioid with adjuvants (e.g. neuropathic component)
- Fast and short-acting drug for breakthrough pain
- Long term NSAIDS not advised in fear of renal damage

Assess at-least annually and adapt the treatment plan.



Chapter – 6: Pregnancy and Sickle Cell disease

Source: Dipty Jain, corresponding author Prachi Atmapoojya, Roshan Colah, and Pooja Lodha, Sickle Cell Disease and Pregnancy, Mediterr J Hematol Infect Dis. 2019; 11(1): e2019040.

Until the 1970s, the management of patients with SCA was weak, and pregnancy was associated with high maternal and fetal mortality. Nowadays with preventive measures such as vaccination and antibiotic prophylaxis since birth, overall disease outcomes and patient survival have improved and there is a significant reduction in maternal and neonatal mortality rates as well. However, despite all the advances, pregnancy in SCD is still associated with higher clinical and obstetric complications compared to the general population.

The physiological adaptations that occur in the circulatory, hematologic, renal and pulmonary systems during pregnancy can overburden organs that already have chronic injuries secondary to SCD, increasing the rate of obstetric complications like eclampsia and pre-eclampsia, worsening of vaso occlusive crises and acute chest syndrome. Though pregnancy in SCD carries a higher risk of maternal and fetal complications, it can be managed by ensuring adequate perinatal care.

Fertility in women with SCD:

SCD patients have delayed physical as well as sexual development. These are consequences of various factors like poor nutrition, repetitive infections, blood transfusions, painful crisis, and frequent hospital admissions. The onset of menarche is delayed in women with SCD and is strongly associated with the HbSS phenotype compared to the HbSC phenotype. Women with SCD have unique risk factors that may affect their ability to conceive, including chronic inflammation, oxidative stress, transfusion-related hemochromatosis, and ovarian sickling, causing ischemia and reperfusion injury to the ovaries.

Another important reason for infertility is hypogonadotropic hypogonadism due to deposition of iron in the hypothalamus-pituitary axis because of multiple blood transfusions and iron overload. A single-center study in Egypt demonstrated that adolescents with SCD and excessive iron stores have significantly lower levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estrogen when compared to those without excessive iron stores.

Like all other organs, intravascular occlusion due to sickling of RBCs can occur in ovaries too, leading to infarction, ovarian dysgenesis, and primary ovarian insufficiency.9 Also, NSAIDs which are very widely used for VOCs in SCD, have been shown to inhibit ovulation in mammalian species, likely due to inhibition of cyclooxygenase 2 (COX-2), thereby reducing prostaglandin synthesis. The result is impairment in ovulation, fertilization, and implantation.

Complications due to SCD in pregnancy:

Obstetric Complications:

- Increased risk of pre-eclampsia and eclampsia. Their incidence is significantly higher in SCD patients as compared to the general population.

- Microvascular damage and decreased uteroplacental circulation in these mothers leads to an exaggerated risk of spontaneous abortions and stillbirths. Other factors contributing to adverse fetal outcomes include poor general health of the mother and drug abuse like tobacco, alcohol and narcotics.16
- Pregnancy exacerbates the pre-existing anaemia in SCD women, leading to a higher incidence of severe anaemia and increased requirement of blood transfusions.
- There is a higher rate of cesarean deliveries in SCD patients, though this disease is not an indication in itself.

Non-Obstetric Complications:

- Further, the incidence of sickle cell disease-related complications like Vaso Occlusive Crisis (VOC), Acute Chest Syndrome (ACS) is increased during pregnancy.
- Defective splenic functions in SCD due to auto-splenectomy, superimposed with the immune-compromised state of pregnancy leads to increased risk of infections like pneumonia, pyelonephritis, UTIs, postpartum infections, etc.
- Pregnancy, by involving a hypercoagulable state, predisposes SCD women to thromboembolic complications like deep vein thrombosis and cerebral venous thrombosis.

Perinatal outcomes:

- Hypoxia and anemia seen in patients with sickle cell disease are important factors that affect fetal growth. Anemia in the mother causes impaired placental perfusion and thereby reduces the nutritional substrate transport and oxygen delivery to the fetus. All this is associated with an increased incidence of IUGR in SCD pregnancy. In low-income countries, other factors like maternal malnutrition, multiple pregnancies, and reduced health care facilities also play a crucial role in adverse perinatal outcomes.
- Incidence of preterm deliveries is high in SCD pregnancy, the exact mechanism is still unclear, but increased production of prostaglandin has been implicated.2 Other reasons for it are anaemia, urinary tract infections, abruption placenta, placenta previa and toxaemia of pregnancy, which are more commonly seen in pregnant women SCD.2
- There is also an increased incidence of other neonatal complications like HIE, RDS, and jaundice in neonates born to SCD mothers leading to increased neonatal admissions. Five-minute APGAR score was compared in an Indian study, it was found that 50% of neonates born to SCD mothers had 5 min APGAR score < 7.

Management of Adverse Events in Pregnancy with SCD

Following major adverse events need planning with effective management for better maternal and neonatal outcomes, as described below:

1. **Painful crisis –** pregnant women presenting with vaso-occlusive crises should be hospitalized, adequate bed rest and fluid intake should be ensured. For pain relief, paracetamol and other NSAIDs should be given. If pain is not relieved narcotic analgesics may be used. Avoid pethidine, as it associated with the risk of seizures.

2. **Acute chest syndrome (ACS) –** Pregnant women with SCD presenting with complaints of severe cough and chest pain should be evaluated for ACS. Pulmonary infiltrates on chest x-ray, leukocytosis, blood, and sputum cultures is done to ascertain infectious complications. Treatment includes appropriate antibiotics, oxygen support, hydration, analgesics and if required blood transfusion.
3. **Hematological Complication –** Anemia is the most common complication of pregnancy. Blood loss, bone marrow suppression by parvovirus infection and nutritional deficiencies are the causes. Transfusions are only indicated when Hb<7gm/dl because such low hemoglobin leads to decreased fetal oxygenation and abnormal fetal outcomes. HELLP syndrome can develop in up to 10% of women with pre-eclampsia. It can be managed conservatively or by urgent delivery depending on gestational age.
4. **Infections** – The major sites of infection are the urinary tract and the respiratory system. Less often, puerperal endometritis, hepatitis, transient bacteremia, osteomyelitis, and HIV have been encountered. During infection, fever and acidosis lead to increased sickling and worsening anaemia. Appropriate antibiotics should be started at the earliest to avoid further complications.

   Acute cholecystitis can also occur during pregnancy and presents with fever, chills, and right upper quadrant pain. Such attacks may simulate sickle hepatopathy, hepatitis or hepatic sequestration. Liver function tests and ultrasound assessment will help in diagnosis. Antibiotics and symptomatic management, followed by elective cholecystectomy, is advised in the postpartum period.
5. **Stroke** – Infarction and hemorrhagic strokes should be suspected in any female presenting with acute neurological impairment. Treatment of choice is emergency exchange transfusion. Thrombolysis is not helpful to treat stroke in SCD.

Pregnancy Management in SCD

Pre-conceptual care

- All women with SCD in reproductive age should be provided with relevant information on how SCD affects pregnancy and what measures should be taken for better maternal and fetal outcomes. It is during this period that she should be made aware of the importance of partner screening and the options for prenatal screening.
- First-trimester prenatal diagnosis by chorionic villus sampling at 10 to 12 weeks of gestation and DNA analysis is the method of choice.31 Often couples at risk are identified late in the second trimester, and they can still be offered amniocentesis at 14–15 weeks gestation and DNA analysis or fetal blood sampling by cordocentesis at 18 to 19 weeks gestation and HPLC analysis of the fetal blood to look for the percentage of adult and sickle hemoglobin present.
- A complete medical and social history of the mother should be obtained, including her vaccination status, current medications, any other co-morbid condition, and any drug abuse.

- Vaccination against all encapsulated organisms, including Neisseria meningitidis, Streptococcus pneumonia, and Haemophilus influenza should be updated. In addition, Hepatitis B and Influenza vaccine should be given.
- Folic acid (5 mg) should be given once daily both preconception and throughout pregnancy. Iron is recommended if there is evidence of iron deficiency, but most of the women have iron overload.
- Most of the women are on hydroxyurea. It is recommended that drugs like hydroxyurea, ACE (angiotensin-converting enzyme) inhibitors, and iron chelators should be discontinued at least 3 months before conception due to the risk of teratogenic side effects.

Antenatal care

- The first prenatal visit should be a comprehensive assessment. Routine blood investigations like complete blood count, HIV, HBs Ag, HCV should be done along with urine examination. Mother should be explained the importance of a regular antenatal visit; it is recommended to visit obstetrician every 15 days during the first two trimesters. Blood pressure and urinalysis should be performed at each consultation, and midstream urine for culture performed monthly as these women are prone to pre-eclampsia and increased risk of urinary tract infections.
- Mothers should be explained to avoid precipitating factors of sickle cell crises such as exposure to extreme temperatures, dehydration, and overexertion. Also, repeated vomiting can cause dehydration and precipitate crisis. Hence, she should seek medical advice at the earliest.
- Women who had PIH/preeclampsia/eclampsia in last pregnancy are advised to take low-dose aspirin 75 mg from 12 weeks of gestation unless they have aspirin sensitivity.
- The transfusion is indicated in case of severe anaemia, and exchange transfusion is recommended in case of stroke and acute chest syndrome.

Intrapartum care

- Delivery of SCD mother should be conducted in a centre equipped with healthcare facilities to manage high-risk pregnancies. Pregnant women with SCD who have a normally growing fetus should be offered elective birth through induction of labour at 38 to 40 weeks of gestation. If there is any indication of impending complications, cesarean delivery should be considered.
- Women should be kept warm and given adequate fluid during labour.
- Pain can be managed with adequate use of analgesics.
- Continuous intrapartum electronic fetal heart rate monitoring is recommended owing to the increased risk of fetal distress.
- Blood should be cross-matched and kept ready at the time of delivery.

Postpartum care

- In the postpartum period, it is crucial to assess the degree of anaemia aggravated by blood loss during labour and delivery, and replacement instituted when indicated.

- Hydration and oxygenation should be maintained, and early mobilization encouraged.
- Crises should be managed as for non-pregnant women. NSAIDs are routinely administered in the postpartum period and can be used during breastfeeding.
- Breastfeeding should be encouraged, as in women without SCD.
- Antithrombotic stockings are also recommended.
- Screening of newborns for sickle haemoglobin is recommended.
- Mother should be advised regarding contraception, progestogen-containing contraceptives such as the progesterone-only pill, injectable contraceptives, and the levonorgestrel intrauterine system are safe and effective in SCD. Estrogen-containing contraceptives should be used as second-line agents. Barrier methods are as safe and effective in women with SCD as in the general population.

Chapter – 7: Sickle Cell Disease Case Presentations

1. Pulmonary Artery Hypertension

32 yrs Shradhha, R/o Keshada, Tah-Simaga, came to OPD with diagnosed sickle cell disease, taking folic acid 5 mg once a day,past history of multiple blood transfusions with complaints of easy fatigability, shortness of breath on exertion for last 1 month.

What additional history will you ask?

- No fever (for sepsis, pneumonia, URI)
- No joint pains (for acute vaso-occlusive crisis)
- No chest pain(for acute chest syndrome)
- No wheeze (for asthma),
- No past h/o TB or TB contact. (for tuberculosis)

What will you look for in Examination?

On examination:

• Afebrile, • Pulse rate - 100/min, • RR-24/min, • BP-106/58 mmHg, • SPO2 on room air 92% • Severe pallor,	• icterus, • +no cyanosis, • no clubbing, • JVP- not raised, • No edema. • No lymph nodes.

PA- Hepatomegaly 5 cms, Splenomegaly 5cms below coastal marines, non-tender.

RS- Rhonchi all over lung fields

CVS- loud P2, soft systolic murmur at left parasternal region.

CNS- wnl.

What's your clinical assessment after history and examination?

Assessment- Sickle cell disease with? mitral regurgitation? Pulmonary artery Hypertension

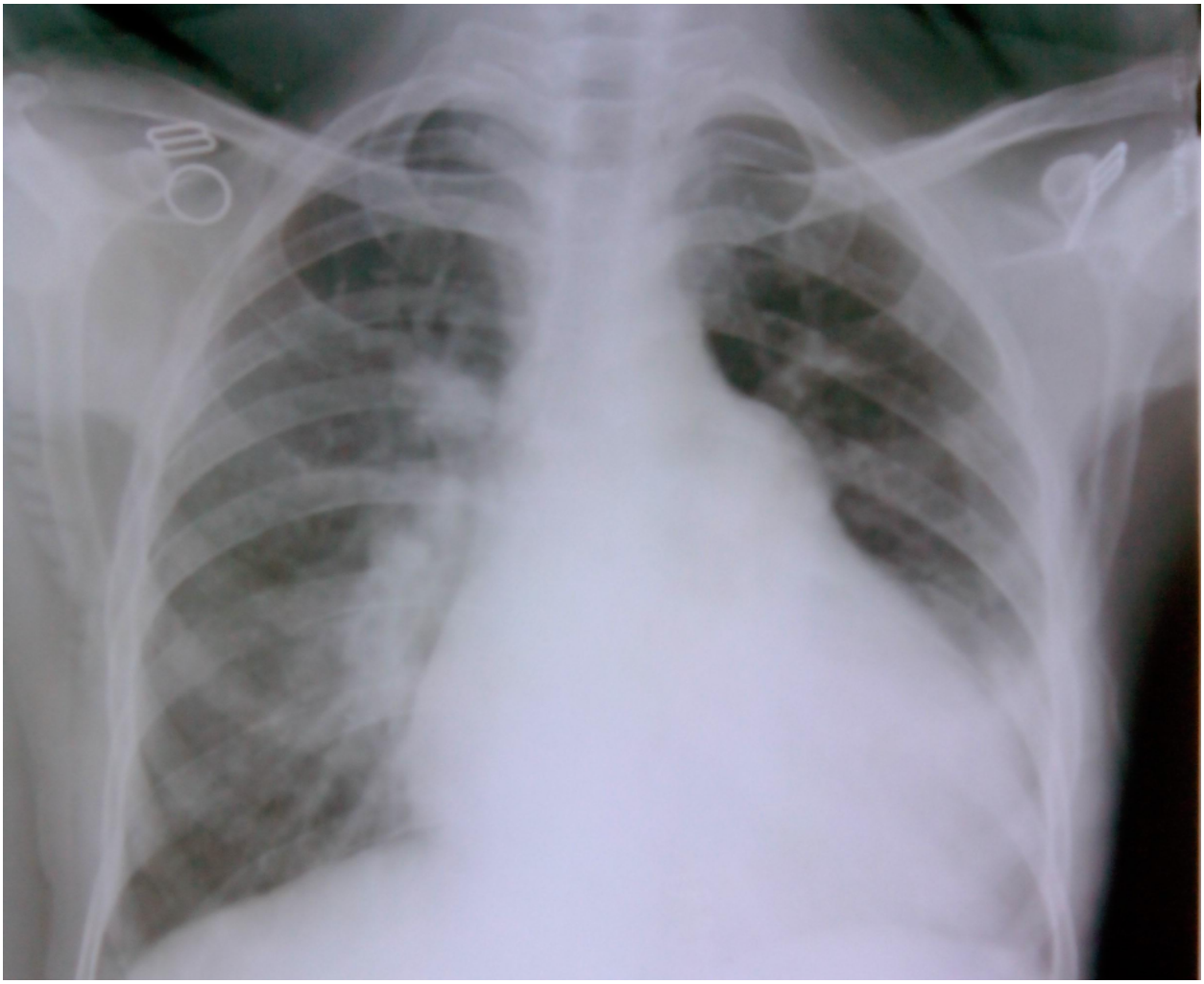
What Labs you will order?

Blood

Haemoglobin (12 - 16)	4.8
Total Leucocyte Count (Blood) (4500 - 11000) cumm	12100.0
Polymorph (40 - 75) %	73.0
Lymphocyte (20 - 40) %	27.0
Eosinophil %	0.0
Platelet Count (100000 - 300000) cumm	156000.0
MCV (75 - 81) per fL	96.6
PS for RBC Morphology	Sickle Cell Anaemia
ANYSOCYTOSIS WITH SEVER HYPOCROMASIA IN ALL MOST CELL MICROCYTS +. MACROCYTS +++.TORGET CELL +.FIXD SICKLE SAPD CELL +++.NO HSP NO BLOST WBC AND PLATLET ADQWET.	
S. ALT (5 - 35) u/L	14.0
Hb Electrophoresis	SS
Sickling Test	Positive

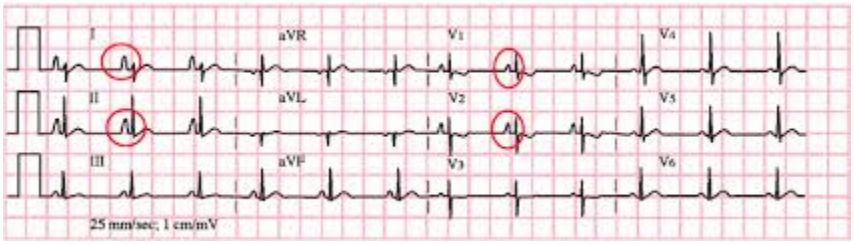
Chest X-Ray:

Positive findings- Prominent PA segment, absence of vessels in lateral lung zones s/o classic Pulmonary arterial hypertension.



ECG:

Positive findings: Tall P waves in lead II s/o P pulmonale



Echo-

Dilated right atrium, RVSP 56+right atrial pressure, mild tricuspid regurgitation, mitral valve normal.

Whats your diagnosis after labs?

Sickle Cell Disease with Pulmonary Arterial Hypertension, severe anemia

How will you treat?

- Counseling for avoiding heavy work,
- Blood transfusion to keep Hb around 10 gm%.

- Cap Hydroxyurea 500mg to start with up titration of dose to achieve desired effect.
- Tab Folic acid 5 mg od
- Tab Furosemide 40 mg od for pulmonary edema.

How's the prognosis?

Pulmonary artery hypertension in sickle cell disease indicates chronic hypoxia due to anemia and has high mortality and morbidity. It is one of the leading causes of death in sickle cell disease. All adults with sickle cell disease should be screened for PAH with loud P2, ECG and if found positive advised Echocardiography.

What would have prevented this complication?

- Early diagnosis of sickle cell disease - was done in this patient.
- Early starting of hydroxyurea - was missed in this case which if would have done early have prevented this complication.

2. Osteomyelitis

16 yrs old Anusuiya, R/o Devari, Tah-Dindauri came to OPD with complaints of pus discharge from right leg below knee for 6 months, started after trauma by iron rod 6 months back, initially developed small ulcer which never healed despite treatment from multiple doctors.

What additional history will you ask?

- No fever (for sepsis)
- No inguinal lumps (for lymph nodes to denote spreading infection)
- No polyuria,polydipsia,polyphagia(for diabetes)
- No past h/o TB or TB contact. (for tuberculosis)
- H/O jaundice in past, H/o Blood transfusion in past (for sickle cell disease)
- No h/o similar illness in siblings.(for sickle cell disease)

What will you look for in Examination?

- Pallor +, no icterus, no cyanosis
- PA- spleen palpable
- CVS, RS- WNL
- Local Exam: Foul smelling discharge from wound located over right upper tibia

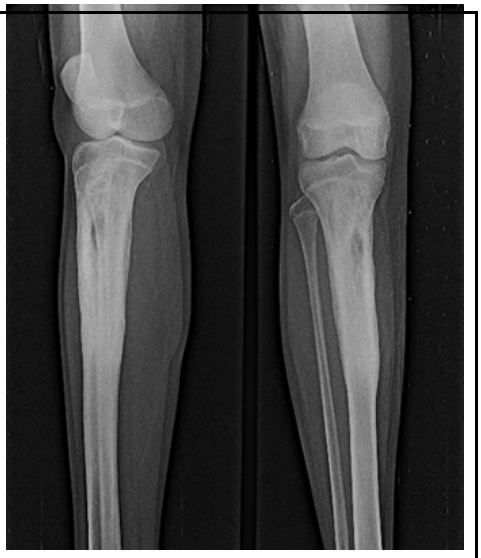
What's your clinical assessment after history and examination?

- Osteomyelitis in a sickle cell disease patient.
- Differentials for osteomyelitis: tubercular, underlying diabetes, foreign body due to trauma.

What Labs you will order?

Blood:

Haemoglobin (12 - 16)	9.3
Total Leucocyte Count (Blood) (4500 - 11000) cumm	7700.0
Polymorph (40 - 75) %	70.0
Lymphocyte (20 - 40) %	28.0
Eosinophil %	2.0
MCV (75 - 81) per fL	76.5



X-ray of Leg:
Positive Findings:
Erosion of bone with periosteal elevation

Whats your diagnosis after labs?
Sickle cell disease with osteomyelitis
In sickle cell disease, initially infarcts happen in bone due to occlusion of RBCs in arteries which later on gets infected to become osteomyelitis. Additionally, due to splenic hypofunction bacterial clearing is less as compared to normal person.

How will you treat this patient?

- Antibiotics (ceftriaxone to cover Salmonella in doses of 80 mg/ kg per day)
- Pain Control
- Hydration
- Start hydroxyurea and folic acid.
- Drainage of Pus

What could have prevented this complication?
Early diagnosis of sickle cell disease
Early starting of hydroxyurea would prevent occlusion of RBCs which prevents infarcts and thus secondary infections.
Treating infections early and aggressively in known sickle cell disease patients

3. Child with infection

6 yrs old Ritaram, R/O Khamariya, Tah-Siltara, presented in OPD with complaints of vomiting for 3 days, loose motions for 3 days,20-25 episodes, watery and abdominal pain for 1 day. Passing urine normally.

What additional history will you ask?

- H/o blood or mucous in stool (for invasive bacterial dysentery, will need antibiotics-ciprofloxacin or cefixime)
- H/o Hydration - taking fluids or not,able to retain fluids or not.
- H/o any treatment received before coming to hospital
- Any danger signs - seizures, persistent vomiting, lethargy, severe dehydration.
- H/o food poisoning - food intake from roadside shop, social gatherings, history of similar symptoms in others members.
- H/o water contamination - h/o symptoms in other family members, water source, chlorination done or not.

What will you look for in Examination?

- Hydration Assessment - mucous membranes like tongue, eyes- dry or moist, presence of sunken eyes, activity - active/dull/lethargy.
- Pallor ++.no icterus, no clubbing. JVP- not raised.
- PA- hepatomegaly +, No splenomegaly.

- RS,CVS assessment.

Whats your clinical assessment after history and examination?

Sickle Cell Diasese with ? acute gastro-enteritis

What Labs you will order?

Blood:

Haemoglobin (12 - 16)	8.0
Total Leucocyte Count (Blood) (4500 - 11000) cumm	7800.0
Polymorph (40 - 75) %	72.0
Lymphocyte (20 - 40) %	28.0
Eosinophil %	0.0
Platelet Count (100000 - 300000) cumm	132000.0

Hb electrophoresis SS

What's your diagnosis after labs?

Sickle Cell Disease with Acute Gastro-enteritis

How will you treat this patient?

- Hydration - first correct dehydration and then maintenance fluids, need to give 1.5 times maintenance fluid than normal patient in sickle cell disease- oral or IV based on patient tolerates orally or not.
- Antibiotics- cefixime(dose 8 mg/kg/day in two divided doses (max 200 mg bd) for 5 days for GI tract infections.
- Start hydroxyurea and folic acid.
- Counselling for water, food and hand hygiene.

4. Child with Severe Anemia

Bhanwardas Chowdhary, 3 years, child brought by parents to OPD with complaints of excessive crying, lethargy and reduced activity for last 15 days.

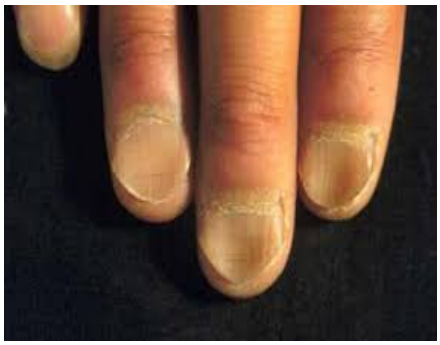
What additional history will you ask?

- History of present Illness- Child was apparently alright 15 days back, gradually became lethargic with reduced activity with no known precipitating cause. Family consulted nearby doctor , was treated with syrups and anti-worm medicines and was told to go to government hospital for treatment of anemia. No bleeding from any sites.
- Bleeding causes of Anemia - No h/o worms in stool, No epistaxis, Gum bleeds, blood in stools (Hemorrhoids or fissure), hematuria or skin rashes.
- Hemolytic causes of anemia- NO h/o definite jaundice (has doubtful history of Jhad-fuk for pilia- not sure if eyes was yellow or not, urine was not yellow), No any lumps in the abdomen(to suggest splenomegaly).
- Congenital causes of anemia- History of stunting or short stature present(prolonged anemia leads to short stature), history of Sibling deaths in early childhood- 3 siblings died at 2-3 years of their age after fever(Because of infections, sepsis in Sickle Cell disease). history of recurrent blood transfusion to parents or any other family members- no history of blood transfusion in family.

- Neoplastic causes of anemia like lymphoma, leukemia- history of swelling in the neck, axilla and groin to suggest lymph node enlargement -Absent.
- History for severity of anemia- pedal swelling, shortness of breath to suggest heart failure -Absent.
- History for certain types of anemia-
    - history of Pica (eating soil, chalk, chuna)- iron Deficiency anemia
    - Strict Vegan diet - B 12 deficiency anemia

What will you look for in Examination?

- Height for Stunting, Weight for wasting.- both stunting and wasting present.
- Severity of Pallor- severe
- Nail changes(Spoon shaped nails(Koilonychia)/ flat nails (Platonychia) for iron deficiency), Knuckle hyperpigmentation for B 12 deficiency anemia- nails normal



- Icterus (to suggest hemolytic nature of anemia)- present
- Lymph Node assessment for leukemia, lymphoma.
- Signs of Heart Failure - raised JVP, tender hepatomegaly, S3 sound on auscultation.
- RS- WNL
- CVS- systolic murmur in all areas
- PA- Splenomegaly 4 cms below the costal margin, no hepatomegaly (please note difference between history and examination.

What's your clinical assessment after history and examination?

Severe anemia possibly sickle cell disease, not in heart failure.

What Labs you will order?

Blood:

Haemoglobin (12 - 16)	5.1
Total Leucocyte Count (Blood) (4500 - 11000) cumm	3300.0
Polymorph (40 - 75) %	70.0
Lymphocyte (20 - 40) %	30.0
Eosinophil %	0.0
Platelet Count (100000 - 300000) cumm	72000.0
MCV (75 - 81) per fL	75.0

Peripheral Smear Examination:

- Anisocytosis with Severe Microcytes & Macrocytes hypochromesia. Pocilocytosis with Tear drop, Pencil cells & Target cells- occ, No Blast, No HSP, No Haemoparacytes seen, fixed Sickle cells +++ & N.RBC seen.
- Platelet - low.
- Retic count- 6%

Whats your diagnosis after labs?

Sickle Cell Disease leading to severe anemia, Pancytopenia. Cause of Pancytopenia needs to be investigated, infections like parvovirus (aplastic crisis) or salmonella typhi are common causes and needs to be treated. WBC count of more than 4000 and platelet count of more than 80000 is required to start hydroxyurea. Associated B 12/Folic acid deficiency can also lead to pancytopenia.

How will you treat this patient?

- Admit for investigating and treating cause of pancytopenia in addition to blood transfusion.
- Blood Transfusion to maintain hemoglobin of 8 Gm% at least.
- Hydroxyurea- To prevent further severe anemia and vaso-occlusive pain crisis after WBC count of more than 4000 and platelet count of more than 80000.

What could have prevented this complication?

Maternal and early newborn screening if mother is diagnosed positive for sickle cell disease during pregnancy could have prevented sibling deaths and severe anemia in this child. Early diagnosis of sickle cell disease and starting of hydroxyurea could have prevented stunting and wasting.

5. Vaso-Ooclusive Pain Crisis

Bhagvat, 14 yrs ,Boy r/o Ganiyari, brought by parents in the emergency room with complaints of severe pain in right upper arm and left leg for the last 2 days. He was well 2 days back, started with fever for 2 days with no localizing symptoms followed by pain in right arm just above the wrist joint and left leg just above left ankle joint severe enough to restrict movements. No swelling, no h/o trauma at that site. No fever.

What additional history will you ask?

- No trauma
- No fever (for sepsis)
- No past h/o TB or TB contact. (for tuberculosis)
- H/O jaundice in past, H/o Blood transfusion in past (for sickle cell disease)
- No h/o similar illness in siblings.(for sickle cell disease)

What will you look for in Examination?

- Temp- Afebrile, Pallor-+++, Icterus++, No clubbing, No cyanosis, No Lymph nodes.
- PA- splenomegaly 3 cms below costal margine.
- RS,CVS- WNL
- Local Exam- Slight redness, raised temperature, Tenderness +, mild swelling +, No draining LN enlargement both in arm and leg.

What's your clinical assessment after history and examination?

- Anemia of possible sickle cell origin with vaso-occlusive pain crisis/ osteomyelitis.
- Pain crisis is the most common presenting complaint of sickle cell disease and should be suspected in any child presenting to OPD/ER with limb/organ pains in endemic region as pain without trauma is uncommon in children.

What Labs you will order?

- Blood:

Haemoglobin (12 - 16)	8.5
Total Leucocyte Count (Blood) (4500 - 11000) cumm	5700.0
Polymorph (40 - 75) %	70.0
Lymphocyte (20 - 40) %	28.0
Eosinophil %	2.0
Platelet Count (100000 - 300000) cumm	199000.0
MCV (75 - 81) per fL	77.6

- Peripheral smear - Anisocytosis with Severe Microcytes, hypochromasia. Poikilocytosis with Tear drop, Pencil cells & Target cells- occ, No Blast, No HSP, No Haemoparacytes seen, fixed Sickle cells +++ & N.RBC seen. Platelet - adequate.
- X ray - Not needed in this case as counts are normal.

What is your diagnosis after labs?

Sickle Cell disease with Vaso-occlusive pain crisis

How will you treat this patient?

Admit for pain management, hydration, prophylactic antibiotics.

- **Pain management:** Principle to be used in sickle cell disease is hit hard and high and then downgrade, so start with opioids(morphine, pentazocine, tramadol) as per highest recommended dose and then downgrade, shift to oral only after full pain control, hydration is achieved.
- **Hydration** - Important to lower viscosity of blood and to resolve crisis, first replenish fluid if dehydrated followed by 1.5 times the normal maintenance fluids. Even with adequate hydration if pain is not resolving one should think of osteomyelitis or abscess, should repeat TLC and blood transfusion may be required even if hemoglobin is above 8/9 Gm% to dilute sickle cell hemoglobin in the body.
- **Start hydroxyurea and folic acid.**
- **Prophylactic Antibiotics**- In vaso-occlusive crisis usually there are areas of ischemia and infarcts which can get easily infected to lead to osteomyelitis or abscesses, prophylactic antibiotics covering salmonella (ceftriaxone /cefixime) should be given during crisis to prevent secondary infections.
- Also look for associate fever, cough, tachypnea (for acute chest syndrome), symptomatic anemia, sequestration (splenic sequestration), stroke etc as vas-occlusive crisis is usually associated with these complications.
- Psychosocial support, distraction, relaxation exercises are useful to reduce need of medicines and early resolution of crisis.

What could have prevented this complication?

- Hydration - especially with fever episodes which precipitates dehydration. Counselling is important at the time of new diagnosis.
- Early diagnosis of sickle cell disease and Early starting of hydroxyurea.
- Repeated vaso-occlusive pain crisis in sickle cell disease can lead to Avascular necrosis (AVN) of femur, auto splenectomy etc.

6. Stroke

23 years old Nalini resident of Sijhaura, With history of 9 months amenorrhea Presented to emergency room with complaints of sudden onset weakness of left side of body since morning. She was apparently alright in morning when she suddenly noticed tingling on left side of body followed by weakness and fall.

What additional history will you ask?

- History of known diabetes, hypertension.(For stroke)
- Family history of diabetes, hypertension, stroke, myocardial infarction.
- History of transient ischemic attacks or weakness in past.
- History of fever, headache (for cerebral malaria)
- History of pedal swelling, hypertension, headache, blurring of vision, epigastric pain (for pregnancy induced hypertension, preeclampsia, eclampsia etc).
- History of photosensitivity, oral ulcers, recurrent abortions (for vasculitis syndromes).
- History of jaundice, blood transfusion, abortion (for sickle cell disease).
- History of chronic cough, fever, weight loss, anorexia, evening rise of temperature, known TB contacts (for CNS tuberculosis).

What will you look for in Examination?

- Afebrile, P - 86/min, BP-110/60 mmHg, RR - 20/Min.
- Pallor +++, no icterus, no clubbing,.
- CNS - well oriented with time, place and person.
- Cranial nerve exam - normal.
- Motor exam -
- Right side - upper and lower limb has normal muscle bulk, power and reflexes.
- Left side - Muscle bulk normal in upper and lower limbs.
- All tendon reflexes brisk on left side with power ⅗ in both upper and lower limb.
- RS, CVS - WNL.
- PA - Fundal height of 34 weeks, cephalic presentation, FHS - 136/Min.

What's your clinical assessment after history and examination?

Stroke in a 34 weeks pregnant lady

What Labs you will order?

- CBC - Hb 9 gm%, TC - 6000, Platelets - 150000
- Urine Albumin - nil.
- Malaria - negative by both rapid kit and peripheral smear.
- SGPT - 35 mg/dl
- Creatinine - 0.5 mg/DL
- Suckling test positive,
- Hb electrophoresis - awaited.
- Peripheral smear - fixed sickle cell +++.

What's your diagnosis after labs?

Cause of stroke in young lady with pregnancy could be sickle cell disease.

Additional tests required- USG for fetal well-being, CT Brain.

How will you treat this patient?

- Blood transfusion simple/exchange
- Aspirin in ischemic stroke
- Thrombolytic therapy not used generally.
- Chronic transfusion and HYDROXYUREA to prevent recurrence.
- Other neurological complications- TIA, seizures, PRES to watch for.
- Start hydroxyurea and folic acid.

What could have prevented this complication?

Early diagnosis before pregnancy and early initiation of hydroxyurea before pregnancy. Hydroxyurea is stopped during pregnancy with repeated blood transfusions if Hb falls below 8 Gm/dl. Prophylactic aspirin may be used to prevent stroke especially with history of previous preeclampsia.

7. Avascular necrosis femoral head

A 30 year old lady Devikunwar Gond who has history of pain in left hip for the last one year, progressively worsening as she cannot squat or stand from sitting position and experiences immense pain while doing these activities. She also gives history of recurrent joint pains for which she has taken some medications as and when needed both as inpatient and on outpatient basis.

A. What additional history would you want to know?

- H/O recurrent blood transfusions, jaundice- YES
- H/O NSAIDs, Steroids, other drugs (chemotherapy), radiotherapy- NSAIDs
- H/O trauma, hip surgery, Tuberculosis, other joint swelling, redness- NO
- Family H/O diseases needing blood transfusion- NO

B. What points would you notice in examination?

- General examination- look for pallor, icterus, hemolytic facies- YES
- Local examination-Inspection- limb shortening(PRESENT), gait (ANTALGIC GAIT)
- Palpation- range of movement at Hip joint (LIMITED AND PAINFUL ABDUCTION & INTERNAL ROTATION)

C. Based on history and examination, what are possible differential diagnosis?

- Hip joint arthritis (Chronic)
- Avascular necrosis femoral head with sickle cell disease
- what investigations would you like to order?
- Hb, sickling test, Hb electrophoresis- Hb- 9g/dl, Sickling test –positive, Electrophoresis- SS pattern
- X-ray left hip AP View, lateral frog leg position

D. what is the final diagnosis based on above findings?

Sickle cell disease with Avascular necrosis head of femur left side

E. How will you treat the patient?

- General management- ensure adequate hydration, rest, NSAIDs/pain management
- Specific management- for sickle cell disease- HYDROXYUREA
- Management for AVN- Early detection, Physiotherapy, reduced weight bearing in early stages
- Late stages- Core decompression, Arthroplasty (high failure rates)

8. Acute chest syndrome

A 16-year-old boy Amit who has history of recurrent blood transfusions and jaundice along with recurrent episodes of joint pains since childhood came to the emergency with complaints of chest pain, breathing difficulty and fever for the last 5 days. He was admitted 6 months ago in the district hospital for multiple joint pains where he was diagnosed to have sickle cell disease (SS pattern).

A. What other history would you want to know?

- H/O Cough with/without sputum. NO
- H/O asthma, past Tuberculosis, previous such episodes/recurrent Pneumonia. NO
- H/O recent episode of VOC. NO

B. what examination findings would you look for?

- General examination- Vitals Temperature- 101F, Pulse- 112/min, Respiratory rate- 36/min, BP 100/70mm Hg, Presence of Cyanosis- ABSENT
- Systemic examination- Inspection- use of accessory muscles, intercostal/subcostal recession (in children)
- Palpation- decreased chest expansion in right infrascapular region
- Percussion- percussion note impaired in right infrascapular region
- Auscultation- air entry decreased in right infrascapular region, inspiratory crepts in the same area

C. Based on the above history and examination findings, what are the possible differential diagnosis?

- Acute Pneumonia
- Acute Chest syndrome

D. What are the investigations you would like to do?

- Spo2- 92% on room air
- Hb- 6g/dl, TLC- 25000/mm3, DLC-Polymorphs-90%, Lymphocytes-10%
- Chest Xray- right lower zone inhomogenous infiltrates

E. What is the probable diagnosis after investigations?

Acute chest syndrome/Acute Pneumonia

F. How will you manage this patient?

- O2 support
- I.V. Antibiotics(For suspected Pneumonia) + I.V. Fluids
- Blood transfusion
- Adequate analgesia
- Start hydroxyurea and folic acid.

9. Sickle cell disease in pregnancy

A 24 year old lady Nirmala Sahu married for last 1 year has amenorrhoea for the last 24 weeks. Her pregnancy was confirmed in a nearby PHC at 10 weeks of gestation and has received Tetanus vaccination and Iron and Folic acid which she took intermittently. She has history of recurrent blood transfusions and multiple hospital admissions for joint pains and body aches since childhood. She now has fever for the last two days along with burning in urine.

What other history would you like to know?

- H/O nausea/vomitting, flank pain or lower abdominal pain. NO
- H/O decreased urine output, blood in urine or change in urine colour. NO
- H/O joint pain, abdominal pain, chest discomfort, breathing difficulty. NO
- H/O facial edema, pedal edema or generalised body swelling. NO

What examination findings would you look for?

- General examination- Vitals- BP- 144/96 mm Hg, Pulse- 100/min, Temperature- 100.4F
- Pallor- Present, Icterus- absent, Pedal edema- present (mild)
- Uterine size- per abdomen- just above the umbilicus
- Renal angle tenderness- absent

What is the likely diagnosis based on the above findings?

Sickle cell disease with Pregnancy induced hypertension with suspected Urinary tract infection with anemia

How will you investigate further?

- Hb- 6.2 g/dl TLC- 15000/mm3 platelet count- 1.8 Lakh/mm3 DLC- Polymorph-90% Lymphocytes- 10%
- Urine WBC- 50-60 pus cells, RBC- 4-5/HPF, Albumin-2+, Sugar- Nil
- Sickling test- Positive, Hb electrophoresis- SS pattern, spo2- 96% on room air

How will you manage this patient?

- Blood transfusions
- Antibiotics for urinary tract infection
- Monitor B.P. and manage with antihypertensive drugs based on monitoring (Alpha methyl dopa, Nifedipine, Labetalol)
- Assess for fetal distress and maturity

What all complications can happen in a pregnant mother with Sickle cell disease?

Maternal-

a. Related to sickle cell disease- infections like UTI, vaso-occlusive crisis, thrombo-embolism.
b. Related to pregnancy- Pregnancy induced hypertension, Post-partum hemorrhage, Ante-partum hemorrhage, Puerperal sepsis
c. **Fetal-** Intrauterine growth retardation, Prematurity.

10. Priapism

21 yrs old Manish, R/O Chakarabhata, came to OPD with complaints of prolonged penile erection for last 1 day.

He was well 2 months back, started with intermittent episodes of erection which used to last for 2 hours and resolve on its own but this time it didn't resolve and was painful.

What additional history will you ask?

- No history of trauma.
- History suggestive of sickle cell disease -
    - History of yellowish discoloration of eyes 2 months back
    - History of stabbing type of chest pain and was admitted in private hospital for the same 2 years back
    - History of received blood transfusion during chest pain episode.
    - History of receiving portion injection multiple times from local practitioner.
    - No history of blood transfusion on family.
    - No sibling deaths in early childhood.
    - No known loud in abdomen.
- No history of unknown bite (Scorpion bite)
- No history of any drug intake.

What will you look for in Examination?

- Afebrile, P 80/min, RR 20/min, BP- 136/90 mmHg, In in pain.
- Pallor ++, mild icterus,, no clubbing, no cyanosis, JVP - normal.
- RS,CVS,PA - WNL.
- Sustained penile erection +++, no scar, no inguinal lymph nodes.

Whats your clinical assessment after history and examination?

Priapism in young man possibly sickle cell disease

What Labs you will order?

Blood:

Haemoglobin (12 - 16)	10.9
Total Leucocyte Count (Blood) (4500 - 11000) cumm	23000.0
Polymorph (40 - 75) %	80.0
Lymphocyte (20 - 40) %	20.0
Eosinophil %	0.0
Platelet Count (100000 - 300000) cumm	353000.0
MCV (75 - 81) per fL	91.8
Creatinine (0.6 - 1.2) mg/dl	0.9

Hb Electrophoresis	
s.takan.	
Sickling Test	Positive
Patient Blood Group	A Positive

Peripheral Smear :

fixed sickle cell +++.

Whats your diagnosis after labs?

Priapism in possible sickle cell disease patient, should be confirmed by Hb electrophoresis, sample for which is taken.

How will you treat this patient?

- Hydration, Analgesia, Start hydroxyurea and folic acid similar to any other sickle cell disease patient.
- It is recommended that treatment should be conservative initially, with the patient being encouraged to urinate, exercise, increase his fluid intake, and take oral analgesics.
- If the episode of priapism persists beyond 2 hours, the patient should report to the emergency department for i.v. hydration and analgesics.
- If the episode persists beyond 4 hours, intracavernosal aspiration and instillation of an α-agonist (injection phenylephrine) should be performed and repeated as needed.
- If the priapism remains for longer than 12 hours, surgery should be considered for shunt placement.
- If left untreated irreversible fibrosis and impotence can occur.

What could have prevented this complication?

Early diagnosis and early initiation of hydroxyurea with folic acid. Counseling of patient about hydration especially in episodes of fever, vomiting, diarrhea, heavy exertion or summers to prevent dehydration and blocking of vessels with sickled red blood cells.

11. Nephropathy Sickle Cell Disease

35y/M Ghanaram Gond from Anuppur with KCO of Sickle cell disease with Hb Electrophoresis pattern of SS; diagnosed in one of the screening camps; not on any medicines came to OPD with C/O

- Edema since 2 months
- Breathlessness with Easy fatigability noted since past 1 & half months.

What WIII you do next?

If stable then further history.

- Vitals: P=98/min; RR= 24/min; Afebrile.
- BP= 144/92mmHg.
- Severe pallor noted; Mild icterus.

What all questions will you ask for??

- Edema_ appeared where?
- Peri-orbital edema first or pedal edema first? - to rule out renal

Involvement:

Breathlessness _ with exertion or without exertion. Which grade? DOE 1 to 4.: to rule out

CVS/anemia:

- Associated orthopnea or PND. : to rule out CVS
- H/O recent fever? Renal involvement

Urine frequency: Whether Nocturia?/Polyuria/Polydipsia? Or Oliguria? Hematuria? - To r/o GNitis or DM.

- Associated nausea & vomiting?: to r/o renal cause or GI cause leading to dehydration

- H/O taking some nephrotoxic drugs? Analgesics?: to rule out renal injury.
- H/O Joint pains or fever or frequent hospitalization?: to r/o SCD or autoimmune etiology.

Patient reported that he noted easy fatigability first & amp; later noted some peri-orbital edema in the morning period which was later followed by the swelling over B/L feet non progressive on nature, pitting type noted since 2 months.

No polyuria/ Nocturia/ Hematuria currently.

Patient told to have polyuria with increased thirst 1-2 years back; & currently, Oliguria noted since long time almost 4-6 months.

- No frothy urine/ skin lesions/ fever in recent past.
- Significant pain, bony mostly; with on & off jaundice, since 10-12 yrs of age.
- Hospitalized at local clinics where fluids were given many times for pain as well as injectable pain killers
- were given frequently since many years.

On examination:

- Pallor significant with Icterus mild.
- CVS: Ejection systolic murmur noted over the Apex. No other complaint.
- RS: Chest clear.
- P/A: No organomegaly noted. Abdomen soft & non-tender.

What D/Ds are you thinking of now??

- Sickle cell Disease with Sickle nephropathy
- DM with nephropathy
- Glomerulonephritis_ ?
- Malaria with CKD
- CKD due to Chronic NSAIDs use.

What investigations will you do now??

- Hb: 3.2 gm%
- MCV: 56/fl
- Sr. Creatinine 4.9mg/dl
- Urine Albumin 3+/ urine Sugar nil
- Serum K= 3.9 mmol/L; Sr. Na 132mmol/L
- USG (KUB):
  - RK: 6.5 x 3.2 cm; LK: 7 x 3.5 cm
  - Poor Cortico-medullary differentiation with No e/o hydroureteronephrosis.

What is Creatinine Clearance? What stage CKD is it??

(weight = 52.4kg)

CrCl= 15.6mL/min.

CKD stage:4

- Stage 1 : Normal or high GFR (GFR > 90 mL/min)
- Stage 2 : Mild CKD (GFR = 60-89 mL/min)
- Stage 3A: Moderate CKD (GFR = 45-59 mL/min)
- Stage 3B: Moderate CKD (GFR = 30-44 mL/min)
- Stage 4: Severe CKD (GFR = 15-29 mL/min)
- Stage 5: End Stage CKD (GFR <15 mL/min)

What is your final diagnosis??

Sickle cell disease with Sickle nephropathy With CKD stage 4.

How will you manage the following patient?

Fluids: restriction advised. Fluids, only when thirsty. Strict urine output advised.

If in crisis then advised for 2/3rd maintenance should be given.

Blood Transfusion: must

Hematinic: Folic acid to avoid the Fe overload

Analgesia: NO NSAIDs now; either opiates or Paracetamol.

Dialysis: no need currently but advisable to enroll in the Dialysis program.

Avoid dehydration; Avoid fever.

Calcium: needs to be added.

Hydroxyurea: can be given based on the CrCl levels

- CrCl ⩾60 mL/minute: No dosage adjustment (of initial dose) necessary.
- CrCl & lt;60 mL/minute: Reduce initial dose by 50% to 7.5 mg/kg/day (Yan 2005); titrate to
- response/avoidance of toxicity (refer to usual dosing).
- ESRD (CrCl & lt; 15mL/min): Reduce initial dose by 50% to 7.5 mg/kg/dose (administer after dialysis on dialysis days); titrate to response/avoidance of toxicity.

Pearls

1. CKD is one of the chronic complications of the SCD.
2. Early institution of the Hydroxyurea will be necessary to avoid the development of chronic complication.
3. CKD with SCD is immunocompromised state and at higher chances of developing the infection, evaluation of the infection must be done.
4. Evaluation of the kidney functions must be done every 2 weekly minimum intervals.

Jan Swasthya Sahyog, Ganiyari

"In thought faith, in deed courage, in life service."

These words, inscribed on a pillar outside the Rashtrapati Bhawan, reflect the simple yet powerful credo of Jan Swasthya Sahyog.

Jan Swasthya Sahyog (JSS) was founded in the year 1996 by a group of like-minded health professionals during their post-graduate studies at the All-India Institute of Medical Sciences (AIIMS), New Dehli. We shared a common desire to do something to change the health situation in rural India, characterized by extreme poverty and lack of access to even the most basic care. Together we decided to develop an effective, low-cost, high quality community-based health care system that would be readily accessible to the rural poor and a model for the delivery of care in low-resource settings.

Our Mission:

To developing a low-cost and effective health program that provides both preventive and curative services in the tribal and rural areas of Bilaspur and surrounding areas of Chhattisgarh in central India. We strongly believe that access to healthcare should not be denied to anyone due to lack of money or due to discrimination on account of caste, sex, religion and social class etc.

We wish to contribute to the health, happiness and well being of the people by:

- Creating a system of primary health care which builds on a continuing and mutually enriching dialogue with the people and derives its strength and long term sustenance from this.

- Providing appropriate rational and low cost health care services delivered with empathy and love. We shall endeavor to make them holistic.
- Identifying problems during our work which demand scientific scrutiny, and working on them on a long term basis.
- Being part of the process of development and rejuvenation of village communities by facilitating efforts to improve education, the environment and the level of sustenance of the people.

We wish to contribute to the sphere of public health in India by:

- Adding to the discourse on public health in India by our experiences in rural Chhattisgarh and our technical, social, and political understanding of them.
- Doing research, which clarifies understanding, examines appropriate solutions which can then be applied by other groups.
- Providing our technical and training skills to people who need them.
- Generating technical literature appropriate to the practice of rural medicine.

We hold dear the following values:

- Honesty, integrity.
- Respect for the poor , the village folk , an understanding of their problems, and an unfailing commitment to them shall inform and permeate all our work.
- Compassion and respect for the wholeness of human beings.

According to the Disability act 2016, Sickle Cell Patients are eligible for the disability certificate. So, being a health worker it's our duty to aware the patient about the disability certificate.

Sickle Cell Patient Helpline –

JSS Anuppur, Madhya Pradesh: 96172 40924

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