

**Hydroxyurea Treatment
for Sickle-cell Disease**



**Training Module For
Medical Officers**

Hydroxyurea Treatment for Sickle-cell Disease

Module Compiled & Edited by

1. Dr. M. H. Pawar, Principal, Public Health Institute, Nagpur
2. Dr. T. C. Parekh, Lecturer
3. Dr. N. B. Rathod, Lecturer
4. Dr. A. Pullawar, Lecturer
5. Dr. P. Ramteke, Lecturer
6. Dr. K. J. Tapdia, M.O.
7. Mr. Amit F. Chavhan, Program Asst.

Sickle-cell

Sickle-cell disease (SCD), or sickle-cell anaemia (or anemia; SCA) or drepanocytosis, is an autosomal recessive genetic blood disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape. Sickling decreases the cells' flexibility and results in a risk of various complications. The sickling occurs because of a mutation in the haemoglobin gene. Life expectancy is shortened, with studies reporting an average life expectancy of 42 in males and 48 in females.

Sickle-cell anaemia is the name of a specific form of sickle-cell disease in which there is homozygosity for the mutation that causes HbS. Sickle-cell anaemia is also referred to as "HbSS", "SS disease", "haemoglobin S" or permutations thereof. In heterozygous people, who have only one sickle gene and one normal adult haemoglobin gene, it is referred to as "HbAS" or "sickle cell trait". Sickle Cell trait (AS) is an inherited condition in which both hemoglobin A and S are produced in the red blood cells, always more A than S. Sickle cell trait is not a type of sickle cell disease. People with sickle cell trait are generally healthy.

Other, rarer forms of sickle-cell disease include sickle-haemoglobin C disease (HbSC), sickle beta-plus-thalassaemia (HbS/ β^+) and sickle beta-zero-thalassaemia (HbS/ β^0). These other forms of sickle-cell disease are compound heterozygous states in which the person has only one copy of the mutation that causes HbS and one copy of another abnormal haemoglobin allele. Different types of sickle cell pattern based on the haemoglobin content is as follows:-

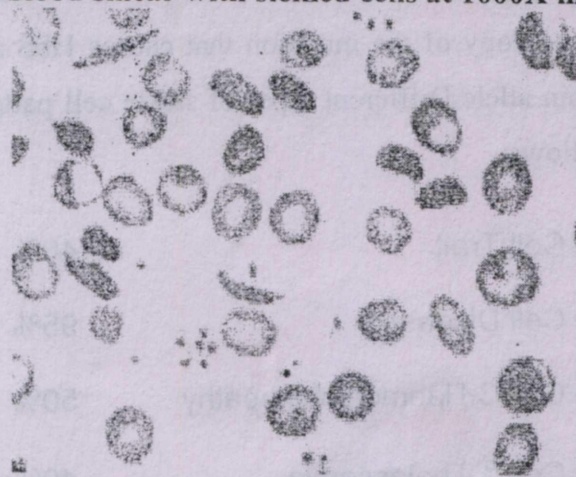
Hb AS	Sickle Cell Trait	40%
Hb SS	Sickle Cell Disease	95%
Hb SC	Sickle Cell C Haemoglobinopathy	50%
Hb BS	Sickle Cell β Thalassemia	40%

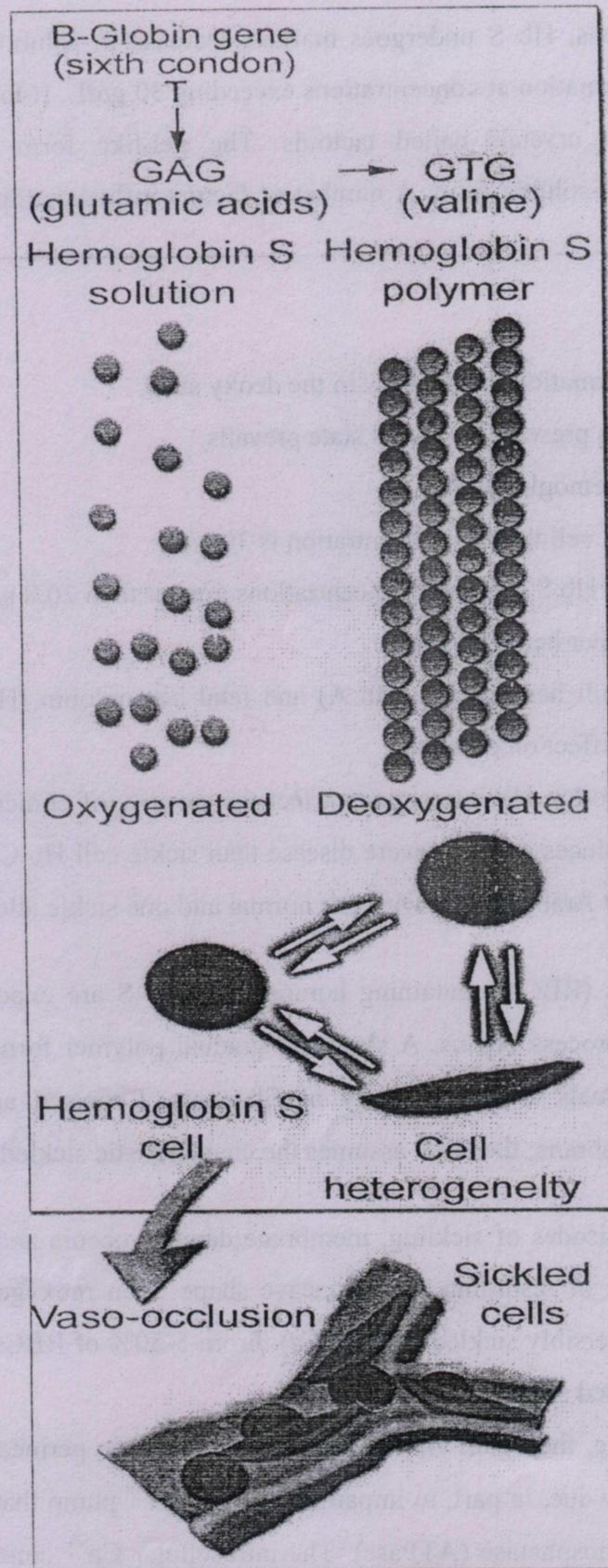
Pathophysiology

This is a hereditary blood disorder due to defective hemoglobin structure. Hemoglobin is a tetramer consisting of two pairs of non-identical globin and polypeptide chains, each chain being associated with one heme group. The heme group is an iron containing pigment responsible for oxygen transport in red blood cells. There are four polypeptide chains (alpha, beta, gamma and delta) in the globin portion. The sequences of amino acids in the alpha, beta, gamma and delta chains are different from each other and very specific for that chain. Sick cell hemoglobin sickling and hence the mutant hemoglobin is called sickle cell hemoglobin (HbS).

Sickle-cell anaemia is caused by a point mutation in the β -globin chain of haemoglobin, causing the hydrophilic amino acid glutamic acid to be replaced with the hydrophobic amino acid valine at the sixth position. The β -globin gene is found on the short arm of chromosome 11. The association of two wild-type α -globin subunits with two mutant β -globin subunits forms haemoglobin S (HbS). Under low-oxygen conditions (being at high altitude, for example), the absence of a polar amino acid at position six of the β -globin chain promotes the non-covalent polymerisation (aggregation) of haemoglobin, which distorts red blood cells into a sickle shape and decreases their elasticity.

Peripheral blood smear with sickled cells at 1000X magnification





Above table shows the Molecular and cellular changes of hemoglobin S.

Under deoxy conditions, Hb S undergoes marked decrease in solubility, increased viscosity, and polymer formation at concentrations exceeding 30 g/dL. It forms a gel-like substance containing Hb crystals called tactoids. The gel-like form of Hb is in equilibrium with its liquid-soluble form. A number of factors influence this equilibrium, including the following:

- Oxygen tension
 - Polymer formation occurs only in the deoxy state.
 - If oxygen is present, the liquid state prevails.
- Concentration of hemoglobin S
 - The normal cellular Hb concentration is 30 g/dL.
 - Gelation of Hb S occurs at concentrations greater than 20.8 g/dL.
- The presence of other hemoglobins
 - Normal adult hemoglobin (Hb A) and fetal hemoglobin (Hb F) have an inhibitory effect on gelation.
 - These and other Hb interactions affect the severity of clinical syndromes. Hb SS produces a more severe disease than sickle cell Hb C (Hb SC), Hb SD, Hb SO Arab, and Hb with one normal and one sickle allele (Hb SA).

When red blood cells (RBCs) containing homozygous Hb S are exposed to deoxy conditions, the sickling process begins. A slow and gradual polymer formation ensues. Electron microscopy reveals a parallel array of filaments. Repeated and prolonged sickling involves the membrane; the RBC assumes the characteristic sickled shape.

- After recurrent episodes of sickling, membrane damage occurs and the cells are no longer capable of resuming the biconcave shape upon reoxygenation. Thus, they become irreversibly sickled cells (ISCs). From 5-50% of RBCs permanently remain in the sickled shape.
- When RBCs sickle, they gain Na^+ and lose K^+ . Membrane permeability to Ca^{++} increases, possibly due, in part, to impairment in the Ca^{++} pump that is dependent on adenosine triphosphatase (ATPase). The intracellular Ca^{++} concentration is 4

times the reference level. The membrane becomes more rigid, possibly due to changes in cytoskeletal protein interactions; however, these changes are not found consistently. Also, whether calcium is responsible for membrane rigidity is not clear.

- Membrane vesicle formation occurs, and the lipid bilayer is perturbed. The outer leaflet has increased amounts of phosphatidyl ethanolamine and contains phosphatidyl serine. The latter may play a role as a contributor to thrombosis, acting as a catalyst for plasma clotting factors. Membrane rigidity can be reversed in vitro by replacing Hb S with Hb A, suggesting that Hb S interacts with the cell membrane.
- Sick cells express very late antigen (VLA)-4 on the surface. VLA-4 interacts with the endothelial cell adhesive molecule, vascular cell adhesive molecule (VCAM)-1. VCAM-1 is upregulated by hypoxia and inhibited by nitric oxide. Hypoxia also decreases nitric oxide production, thereby adding to the adhesion of sick cells to the vascular endothelium. Nitric oxide is a vasodilator. Free Hb is an avid scavenger of nitric oxide. Because of the continuing active hemolysis, there is free Hb in the plasma, and it scavenges nitric oxide. This makes it less available and contributes to vasoconstriction.
- Sick RBCs adhere to endothelium because of increased stickiness. The endothelium participates in this process as do neutrophils, which also express increased levels of adhesive molecules.
- Deformable sick cells express CD18 and adhere abnormally to endothelium up to 10 times more than normal cells, while ISC cells do not. As paradoxical as it might seem, individuals who produce large numbers of ISC cells have fewer vasoocclusive crises than those with more deformable RBCs.
- Sick cells also adhere to macrophages. This property may contribute to erythrophagocytosis and the hemolytic process. The microvascular perfusion at the level of the prearterioles is influenced by RBCs containing Hb S polymers. This occurs at arterial oxygen saturation, before any morphologic change is apparent.

- Hemolysis is a constant finding in sickle cell syndromes. Approximately one third of RBCs undergo intravascular hemolysis, possibly due to loss of membrane filaments during oxygenation and deoxygenation. The remainder hemolyze by erythrophagocytosis by macrophages. This process can be partially modified by Fc (crystallizable fragment) blockade, suggesting that the process can be mediated by immune mechanisms.
- Sickie RBCs have increased immunoglobulin G (IgG) on the cell surface. Vasoocclusive crisis is often triggered by infection. Levels of fibrinogen and fibronectin and the D-dimer are elevated in these patients. Plasma clotting factors likely participate in the microthrombi in the prearterioles.
- These physiological changes result in a disease with the following cardinal signs: (1) hemolytic anemia, (2) painful vasoocclusive crisis, and (3) multiple organ damage with microinfarcts, including heart, skeleton, spleen, and central nervous system.

Capillary Flow of Normal and Sickie Red Cells

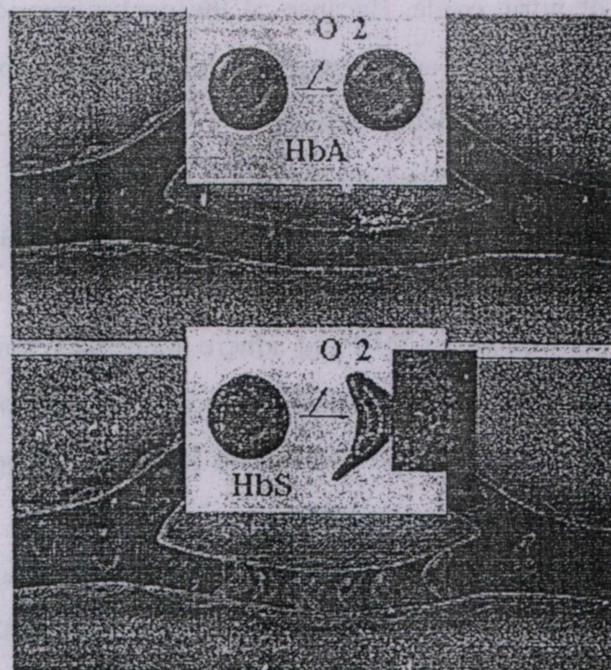
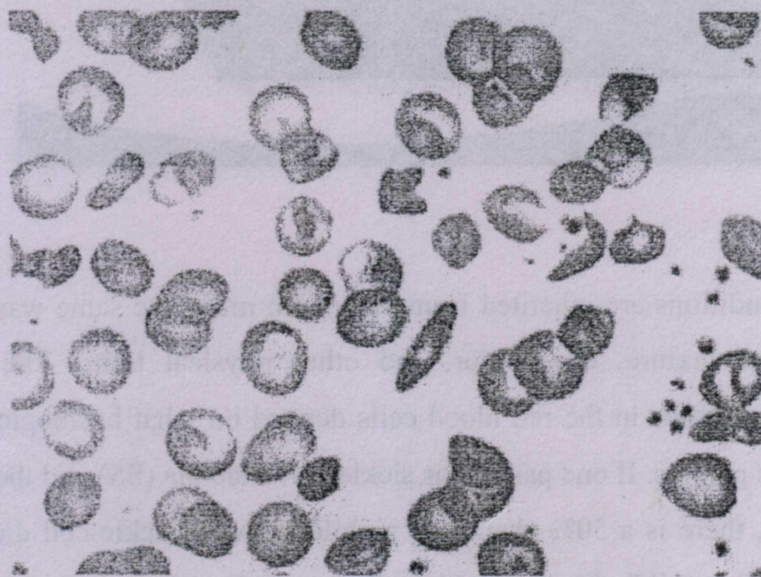


Figure 4. Normal red cells maintain their shape as they pass through the capillaries and release oxygen to the peripheral tissues (upper panel). Hemoglobin polymers form in the sickle cell cells with oxygen release, causing them to deform. The

deformed cells block the flow of cells and interrupt the delivery of oxygen to the tissues (lower panel).

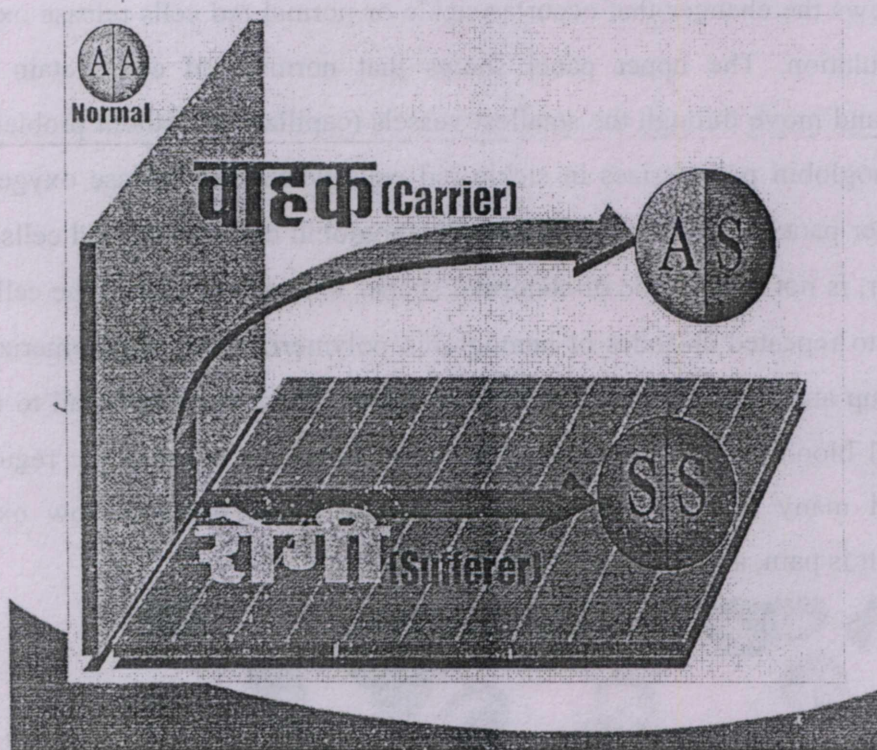
Figure shows the changes that occur as sickle or normal red cells release oxygen in the microcirculation. The upper panel shows that normal red cells retain their biconcave shape and move through the smallest vessels (capillaries) without problem. In contrast, the hemoglobin polymerizes in sickle red cells when they release oxygen, as shown in the lower panel. The polymerization of hemoglobin deforms the red cells. The problem, however, is not simply one of abnormal shape. The membranes of the cells are rigid due in part to repeated episodes of hemoglobin polymerization / depolymerization as the cells pick up and release oxygen in the circulation. These rigid cells fail to move through the small blood vessels, blocking local blood flow to a microscopic region of tissue. Amplified many times, these episodes produce tissue hypoxia (low oxygen supply). The result is pain, and often damage to organs.



Peripheral blood smear with Howell-Jolly body, indicating functional asplenia.

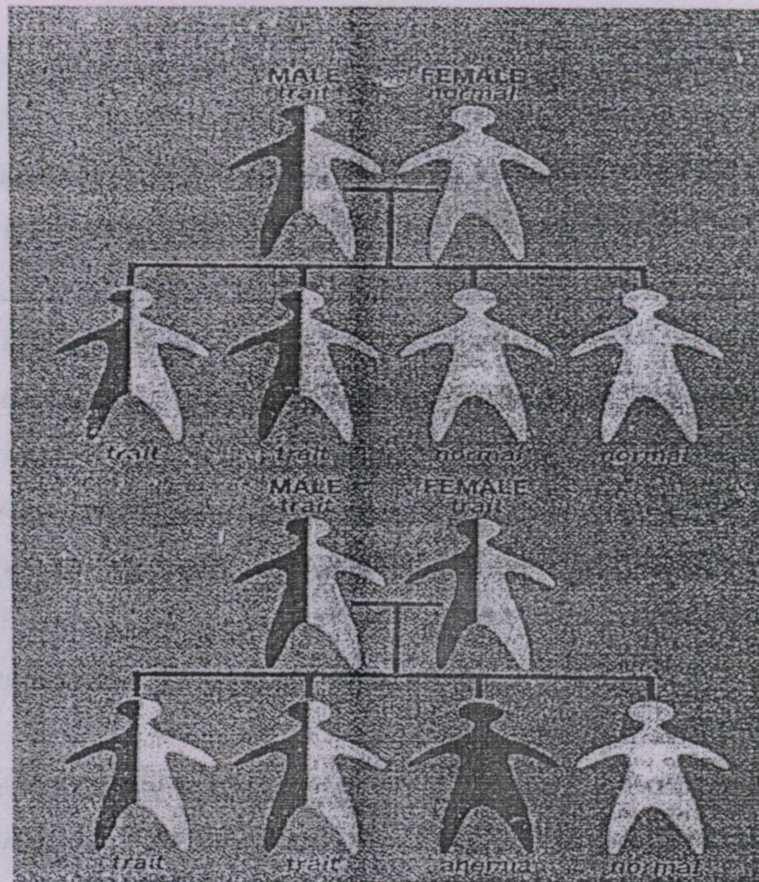
The damage to red cell membranes promotes many of the complications of sickle cell disease. The anemia in sickle cell disease is caused by red cell destruction, or hemolysis. The production of red cells by the bone marrow increases dramatically, but is unable to keep pace with the destruction. Red cell production increases by five to ten-folds in most patients with sickle cell disease. The average half-life of normal red cells is about 40 days. In patients with sickle cell disease, this value can fall to as low as four days. The

volume of "active" bone marrow is much greater than normal in patients with sickle cell disease due to the demand for greater red cell production. The degree of anemia varies widely between patients.



Inheritance

Sickle-cell conditions are inherited from parents in much the same way as blood type, hair colour and texture, eye colour, and other physical traits. The types of haemoglobin a person makes in the red blood cells depend on what haemoglobin genes are inherited from his parents. If one parent has sickle-cell anaemia (SS) and the other has sickle-cell trait (AS), there is a 50% chance of a child's having sickle-cell disease (SS) and a 50% chance of a child's having sickle-cell trait (AS). When both parents have sickle-cell trait (AS), a child has a 25% chance (1 of 4) of sickle-cell disease (SS), as shown in the diagram.



Race

SCD is present mostly in blacks. It also is found, with much less frequency, in eastern Mediterranean and Middle East populations.

Sex

The male-to-female ratio is 1:1.

Age

SCD is a lifelong condition. It first manifests in the second half of the first year of life and persists for the entire lifespan.

Sickle Cell Disorder and the State of Maharashtra

Studies carried out indicates that the overall prevalence of sickle cell disorder in different tribal populations is 10% for carrier state and 0.5% for the sufferer. The total tribal population from the State of Maharashtra as per the recent Govt. record is 90 lakhs at the end of the 20th century [Note: lakh equals 100,000. -KRB]. Based on this number, the expected carriers of sickle cell would be 9 lakhs and expected number of sickle cell homozygotes would be 45,000. The prevalence is very high among the Bhil and Pawara tribal groups from the Nandurbar District and the Madia, Pardhan, Otkar and Gond from the Gadchiroli District. It is estimated that there are more than 10,000 sickle cell patients in the Nandurbar District itself. The Gadchiroli District is expected to have more than 5,000. Taking into consideration the problem of sickle cell disorder, government of Maharashtra has launched a Sickle cell disease control program among high risk tribal populations in the 12 districts of the State of Maharashtra. Provide diagnostic facilities for sickle cell disorder and other genetic defects.

During the last ten years, based on the population genetic surveys in different tribal areas of Maharashtra using these rapid cost-effective laboratory techniques. Population genetic survey data from our Dept. indicates that the prevalence of sickle cell disorder in the overall population of Maharashtra is less than 0.1% while it is very high amongst the tribal population groups from Nandurbar and Gadchiroli districts of the State. The same tribal population groups residing in the neighboring states of Gujarat, Madhya Pradesh and Andhra Pradesh have a similar prevalence. Epidemiological data suggests:

1. Prevalence of sickle cell disorder is very high among tribal population groups Bhil and Pawara from Nandurbar Dist. and amongst the Madia, Pardhan and Otkar population from Gadchiroli Dist. I.e. 20 - 20%.
2. The highest recorded prevalence is among the Otkar group i.e. 35%.
3. The sickle cell gene is practically absent among the Mahadeo Koli, Thakar and other tribal groups from Western Maharashtra.
4. The overall prevalence among tribal populations is about 10% for the carrier state and 0.5% for sufferers.

Common symptoms in sickle cell patient

Some of the common symptoms seen in patients suffering from sickle cell anaemia include:

- * Anaemia
- * Intermittent Jaundice
- * Severe joint pains
- * Recurrent infections

These symptoms usually appear between the ages of four and five and severity increases with age. Most of the patients do not require blood transfusion. Careful history, presence of the above mentioned symptoms and caste constitute basis for diagnosis. Physical findings are not specific.

- o Scleral icterus is present, and, upon ophthalmoscopic examination of the conjunctiva with the +40 lens, abnormal or corkscrew-shaped blood vessels may be seen.
- o The mucous membranes are pale.
- o A systolic murmur may be heard over the entire precordium.
- o In childhood, splenomegaly is present, although this is not present in adults due to autosplenectomy. In adulthood, leg ulcers may be found over the malleoli sickle cell anemia.

Complications

Sickle-cell anaemia can lead to various complications, including:

Sickle cell crisis

The term "sickle cell crisis" is used to describe several independent acute conditions occurring in patients with sickle cell disease. Sickle cell disease results in anaemia and crisis that could be of many types including The vaso-occlusive crisis, aplastic crisis, sequestration crisis, hyper haemolytic crisis and others. Most episodes of sickle cell crises last between five and seven days.

Vaso-occlusive crisis

The vaso-occlusive crisis is caused by sickle-shaped red blood cells that obstruct capillaries and restrict blood flow to an organ, resulting in ischaemia, pain, necrosis and often organ damage. The frequency, severity, and duration of these crises vary considerably. Painful crises are treated with hydration and analgesics; pain management requires opioid administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manage on NSAIDs (such as diclofenac or naproxen). For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia (PCA) devices are commonly used in this setting. Diphenhydramine is sometimes effective for the itching associated with the opioid use. Incentive spirometry, a technique to encourage deep breathing to minimise the development of atelectasis, is recommended.

Splenic sequestration crisis

Because of its narrow vessels and function in clearing defective red blood cells, the spleen is frequently affected. It is usually infarcted before the end of childhood in individuals suffering from sickle-cell anaemia. This autosplenectomy increases the risk of infection from encapsulated organisms; preventive antibiotics and vaccinations are recommended for those with such asplenia. *Splenic sequestration crises*: are acute, painful enlargements of the spleen. The sinusoids and gates would open at the same time resulting in sudden pooling of the blood into the spleen and circulatory defect leading to

sudden hypovolaemia. The abdomen becomes bloated and very hard. Splenic sequestration crises is considered an emergency. If not treated, patients may die within 1–2 hours due to circulatory failure. Management is supportive, sometimes with blood transfusion. This crisis is transient, it continues for 3–4 hours and may last for one day.

Aplastic crisis

Aplastic crises are acute worsenings of the patient's baseline anaemia, producing pallor, tachycardia, and fatigue. This crisis is triggered by parvovirus B19, which directly affects erythropoiesis (production of red blood cells) by invading the red cell precursors and multiplying in them and destroying them. Parvovirus infection nearly completely prevents red blood cell production for two to three days. In normal individuals, this is of little consequence, but the shortened red cell life of sickle-cell patients results in an abrupt, life-threatening situation. Reticulocyte counts drop dramatically during the disease (causing reticulocytopenia), and the rapid turnover of red cells leads to the drop in haemoglobin. This crisis takes 4 days to one week to disappear. Most patients can be managed supportively; some need blood transfusion.

Haemolytic crisis

Haemolytic crises are acute accelerated drops in haemoglobin level. The red blood cells break down at a faster rate. This is particularly common in patients with co-existent G6PD deficiency. Management is supportive, sometimes with blood transfusions.

Other complications

- Overwhelming **post-(auto)splenectomy infection (OPSI)**, which is due to functional asplenia, caused by encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Daily penicillin prophylaxis is the most commonly used treatment during childhood, with some haematologists (hematologists) continuing treatment indefinitely. Patients benefit today from routine vaccination for *H. influenzae*, *S. pneumoniae*, and *Neisseria meningitidis*.

- **Stroke**, which can result from a progressive narrowing of blood vessels, preventing oxygen from reaching the brain. Cerebral infarction occurs in children and cerebral haemorrhage in adults.
- **Cholelithiasis (gallstones) and cholecystitis**, which may result from excessive bilirubin production and precipitation due to prolonged haemolysis.
- **Avascular necrosis** (aseptic bone necrosis) of the hip and other major joints, which may occur as a result of ischaemia.
- Decreased immune reactions due to hyposplenism (malfunctioning of the spleen).
- **Priapism** and infarction of the penis.
- **Osteomyelitis** (bacterial bone infection); the most common cause of osteomyelitis in sickle cell disease is *Salmonella* (especially the non-typical serotypes *Salmonella typhimurium*, *Salmonella enteritidis*, *Salmonella choleraesuis* and *Salmonella paratyphi B*), followed by *Staphylococcus aureus* and Gram-negative enteric bacilli perhaps because intravascular sickling of the bowel leads to patchy ischaemic infarction.
- Opioid tolerance, which can occur as a normal, physiologic response to the therapeutic use of opiates. Addiction to opiates occurs no more commonly among individuals with sickle-cell disease than among other individuals treated with opiates for other reasons.
- Acute papillary necrosis in the kidneys.
- Leg ulcers.
- In eyes, background retinopathy, proliferative retinopathy, vitreous haemorrhages and retinal detachments, resulting in blindness. Regular annual eye checks are recommended.
- **During pregnancy**, intrauterine growth retardation, spontaneous abortion, and pre-eclampsia.
- **Chronic pain**: Even in the absence of acute vaso-occlusive pain, many patients have chronic pain that is not reported.
- **Pulmonary hypertension** (increased pressure on the pulmonary artery), leading to strain on the right ventricle and a risk of heart failure; typical symptoms are shortness of breath, decreased exercise tolerance and episodes of syncope.

Diagnosis

Diagnosis based on the symptoms

Some of the common symptoms seen in patients suffering from sickle cell anaemia include:

- * Anaemia
- * Intermittent Jaundice
- * Severe joint pains
- * Recurrent infections

These symptoms usually appear between the ages of four and five and severity increases with age. Most of the patients do not require blood transfusion. Careful history, presence of the above mentioned symptoms and caste constitute basis for diagnosis of sickle cell anemia.

Diagnosis of sickle cell carriers and sufferers is possible by careful clinical examination of the patient supported by laboratory investigations.

In HbSS, the full blood count reveals haemoglobin levels in the range of 6-8 g/dL with a high reticulocyte count (as the bone marrow compensates for the destruction of sickle cells by producing more red blood cells). In other forms of sickle-cell disease, Hb levels tend to be higher. A blood film may show features of hyposplenism (target cells and Howell-Jolly bodies).

Sickling of the red blood cells, on a blood film, can be induced by the addition of sodium metabisulfite. The presence of sickle haemoglobin can also be demonstrated with the "sickle solubility test". A mixture of haemoglobin S (Hb S) in a reducing solution (such as sodium dithionite) gives a turbid appearance, whereas normal Hb gives a clear solution.

Abnormal haemoglobin forms can be detected on haemoglobin electrophoresis, a form of gel electrophoresis on which the various types of haemoglobin move at varying

- **Chronic renal failure** due to Sickle cell nephropathy—manifests itself with hypertension (high blood pressure), proteinuria (protein loss in the urine), haematuria (loss of red blood cells in urine) and worsened anaemia. If it progresses to end-stage renal failure, it carries a poor prognosis.

Management

1. Folic acid

Children born with sickle-cell disease will undergo close observation by the paediatrician and will require management by a haematologist to assure they remain healthy.

These patients will take following **prophylactic** doses of folic acid as per their age daily for life.

< 1 Year - 1Mg

< 2 Year - 2.5 Mg

> 2 Year - 5 Mg

Theurapeutic dose of folic acid is to given if P.S. is showing macrocytes & /or MCHC is more than normal

If the patient is severly anaemic , then Inj. B12 can be given.

2. Penicillin

penicillin prophylaxis should be given to sickle cell disease patients.dose schedule is as follows:-

<3 yrs age- 125 mg b.d.

>3 yrs age -250 mg b.d.

If hypersensitivity to pencillin, then give erythromycin as 10 mg/kg body weight

3. Painful (vaso-occlusive) crisis

Painful crises are treated symptomatically with analgesics; pain management requires opioid administration at regular intervals until the crisis has settled. **For milder crises**, a subgroup of patients manage on NSAIDs (such as diclofenac or naproxen). **For more severe crises**, most patients require inpatient management for intravenous opioids; patient-controlled analgesia (PCA) devices are commonly used in this setting. Diphenhydramine is also an effective agent that is frequently prescribed by doctors in order to help control any itching associated with the use of opioids.

speeds. Sickle-cell haemoglobin (HgbS) and haemoglobin C with sickling (HgbSC)—the two most common forms—can be identified from there. The diagnosis can be confirmed with high-performance liquid chromatography (HPLC). Genetic testing is rarely performed, as other investigations are highly specific for HbS and HbC.

An acute sickle-cell crisis is often precipitated by infection. Therefore, a urinalysis to detect an occult urinary tract infection, and chest X-ray to look for occult pneumonia should be routinely performed.

For developing countries like India, simple, rapid and inexpensive yet reliable laboratory tests are necessary, particularly, when screening has to be carried out on large populations located in geographically difficult areas. Such techniques have been developed in our Dept. that are suitable for field work and require minimum amount of blood (only a few drops). The results are available within half an hour and the test is very cost effective. The tests include:

Solubility test

Hb Electrophoresis/HPLC

* After the patients receives blood transfusion – NO TEST FOR THE DIAGNOSIS OF SICKLE CELL SHOULD BE DONE FOR NEXT THREE MONTHS.

* Solubility test should not be done in children < one year age as Hb F is more in them.

* In cases of severe anemia test may be false negative and hence should be repeated.

Other Investigations necessary before starting the treatment in Sickle Cell disease patients. :-

- 1) HB % , CBC
- 2) Peripheral Smear
- 3) Reticulocyte count
- 4) KFT/LFT
- 5) CT Scan if necessary

Hydroxyurea

The first approved drug for the causative treatment of sickle-cell anaemia, hydroxyurea, was shown to decrease the number and severity of attacks in a study in 1995 (Charache *et al.*) and shown to possibly increase survival time in a study in 2003 (Steinberg *et al.*). This is achieved, in part, by reactivating fetal haemoglobin production in place of the haemoglobin S that causes sickle-cell anaemia. Hydroxyurea had previously been used as a chemotherapy agent, and there is some concern that long-term use may be harmful, but this risk has been shown to be either absent or very small and it is likely that the benefits outweigh the risks.

Hydroxyurea Protocol

Higher levels of fetal hemoglobin (Hb F) and lower leukocyte counts are thought to be beneficial in patients with sickle cell disease and can be achieved with daily oral administration of hydroxyurea (HU). A placebo-controlled, double-blind, prospective trial in severely affected adults with Hb SS showed that HU significantly reduced the incidence of vaso-occlusive pain, acute chest syndrome, and blood transfusions.⁷⁵ A multi-center phase I/II trial in children > 5 years-of-age showed safety and hematological effects similar to those observed in adults.⁷⁶ Clinical benefit in children with Hb SS has been suggested by a number of open-label trials.⁷⁷⁻⁸² The drug is approved with the important caution that the drug is not curative and requires close hematologic monitoring for myelotoxicity and the strict use of contraception by both men and women who are sexually active. Use of HU in patients with Hb SC or S β^+ thalassemia is under investigation.

The clinical course of each patient with sickle cell disease should be regularly reviewed by a pediatric hematologist/sickle cell program and the possibility of hydroxyurea treatment and its pro and cons considered. Many patients with severe complications may also be candidates for either a program of chronic transfusions or, if an HLA matched sibling is available, stem cell transplantation. HU is generally not considered appropriate for patients with stroke, and it is not useful in the treatment of acute sickle pain. No improvement is expected until the drug has been taken daily for 3-6 months. HU may alter the natural history of the sickle cell disease; for example

Acute chest crisis

Management is similar to vaso-occlusive crisis, with the addition of antibiotics (usually a quinolone or macrolide, since wall-deficient ["atypical"] bacteria are thought to contribute to the syndrome), oxygen supplementation for hypoxia, and close observation. Should the pulmonary infiltrate worsen or the oxygen requirements increase, simple blood transfusion or exchange transfusion is indicated. The latter involves the exchange of a significant portion of the patient's red cell mass for normal red cells, which decreases the percent of haemoglobin S in the patient's blood.

2. Fractionated bilirubin, ALT, and creatinine: baseline, then every 24 weeks.
If Change in values of $> 25\%$ of the baseline (which is considered as normal) at the start of treatment. ---- IMMEDIATELY STOP THE TREATMENT. WITHHOLD FOR THREE TO SIX WEEK AND THEN DECIDE FURTHER TREATMENT.
3. History and physical examination: baseline, then every 4 weeks until maximum dose tolerated for 8-12 weeks, then every 8 weeks. Be alert to the possibility of recurrent or new splenomegaly and risk of splenic sequestration.

If you are not able to monitor the routine investigations of the patients or have a doubt about patients compliance and follow up don't start the treatment .

Before taking hydroxyurea

- Tell your doctor and pharmacist if you are allergic to hydroxyurea, any other medications, or any of the inactive ingredients in hydroxyurea capsules. Ask your pharmacist for a list of the ingredients.
- Tell your doctor if you are taking or have ever taken an interferon. (Interferons are a group of medications similar to substances produced by the body. They are used to treat diseases that involve the immune system such as certain types of cancer, hepatitis, multiple sclerosis, and genital warts. If you are taking or have ever taken an interferon, there is a greater chance that you will develop severe skin problems during your treatment with hydroxyurea. Ask your doctor or pharmacist if you are not sure if you are taking or have ever taken an interferon.
- Tell your doctor and pharmacist what prescription and nonprescription medications, vitamins, nutritional supplements, and herbal products you are taking or plan to take. Be sure to mention any of the following: medications to treat human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), especially didanosine and stavudine; probenecid; or sulfinpyrazone. Your doctor may need to change the doses of your medications or monitor you carefully for side effects.

splenomegaly or splenic sequestration may occur in relatively older patients. HU is a potentially toxic chemotherapeutic agent whose long term toxicity (including concerns about carcinogenicity and teratogenicity) is unresolved. *Thus the drug should be initiated and monitored only by hematologists with expertise in chemotherapy and sickle cell disease and after written documentation of patient education and consent.*

Indications (Inclusion criteria)

Dx : Hb SS or S β^0 – thalassemia

1. >-5 years - of – age
2. >- 3 Hospital admission for severe vaso – occlusive pain events or blood transfusion

ONLY (Hospital admission due to secondary infections episode should not be considered as a criteria)

3. If there is Avascular necrosis in children > - 5 years age.
4. Central nervous system symptoms like stroke.

Exclusion criteria

1. HIV Positive patient
2. HBSAg Positive
3. Any abnormal laboratory test

Pregnancy, Inability to use reliable contraception if sexually active (men and women)
Inability to comply with daily dosing and frequent laboratory monitoring are also considered as a exclusion criteria depending on the patient.

Dosage

Hydroxyurea 10 mg/ kg p.o. q.d. (500 mg capsules).

Monitoring

1. Baseline - CBC,

reticulocyte count:

LFT

KFT

HIV

HBsAg

every 4 weeks until maximum dose tolerated without toxicity .

Toxicity

Toxicity from hydroxyurea is generally defined as any of the following:

ANC $<2000 \times 10^6/L$

Platelet count $<80,000 \times 10^6/L$

Absolute reticulocyte count $<80,000 \times 10^6/L$ if hemoglobin <9.0 gm/dl Hemoglobin <5 gm/dl or $> 20\%$ below baseline 100% increase in ALT if toxicity occurs, treatment will be stopped for at least 1 week and until toxicity resolves. HU will then be resumed at the same dose or a dose decreased by 2.5-5 mg/kg/d. If toxicity does not recur after 12 wks on the lower dose, the dose may then be increased by 2.5-5 mg/kg/d. If toxicity recurs on the higher dose, then HU will be stopped again until toxicity resolves, and hydroxyurea can then be resumed at the lower dose.

Treatment Details

- Baseline measurements- At least two months of baseline information on the hematologic status of patients with sickle cell disease should be available before starting treatment.
- Starting dose- hydroxyurea can be started at a dose of 10 mg/kg orally, on a daily basis. The patient's hematologic status should be monitored to rule-out falls in the neutrophil count to less than 2,500 per cubic millimeter or platelet count to less than 80,000 per cubic millimeter.
- Dose escalation- The dose of hydroxyurea can be increased at a rate of 5 mg/kg/wk as long as the hematologic values remain in an acceptable range, and the patient shows no other evidence of side-effect from the HU, which is done rarely in Indian set-up.
- Maximum dose- At BWH, the maximum dose of hydroxyurea used in most patients is 25 mg/kg/day. Patients at some institutions receive doses of hydroxyurea as high as 35 mg/kg/day. The minimum effective dose of hydroxyurea is one of the unanswered questions from the MSH study. The patients received "maximum tolerated doses" (MTD) in the study. To achieve this, the dose of hydroxyurea was advanced until evidence of BM suppression appeared.

- Tell your doctor if you have human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS); if you are being treated with or have ever been treated with radiation therapy or cancer chemotherapy; or if you have or have ever had kidney, or liver disease.
- Tell your doctor if you are breast-feeding. You should not breast-feed during your treatment with hydroxyurea.
- Your doctor may prescribe a folic acid supplement for you to take during your treatment with hydroxyurea. Take this medication exactly as directed.
- You should know that hydroxyurea may be harmful if it gets on the skin. People who are not taking hydroxyurea should avoid touching hydroxyurea capsules or the bottle that contains the capsules. Always wear disposable gloves when handling hydroxyurea capsules or bottles containing hydroxyurea capsules and wash your hands before and after you touch the bottle or capsules. If the powder from a capsule spills, wipe it up immediately with a damp disposable towel, place the towel in a closed container, such as a plastic bag and throw it away in a trash can that is out of the reach of children and pets.

Hydroxyurea may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away:

- nausea
- vomiting
- diarrhea
- constipation
- drowsiness

Some side effects can be serious. If you experience any of the following symptoms, or those listed in the IMPORTANT WARNING section, call your doctor immediately.

- rash
- purple, blue, or black discoloration of the skin or nails
- loss of feeling in one area of the body
- sores on the skin or in the mouth
- foul-smelling substance oozing from the skin
- swelling of the hands, feet, ankles, or lower legs

Hydroxyurea may cause other side effects. Call your doctor if you have any unusual problems while taking this medication.

Other Sickle Syndromes

Sickle β -thalassemia

Patients with this compound heterozygous condition were excluded from the MSH study. Therefore, no firm data exists on their response to hydroxyurea. Since patients with sickle β -thalassemia often have a substantial quantity of HbA, clinical amelioration for a given degree of elevation of Hb F might be greater than that seen in patients with homozygous sickle cell anemia. Symptomatic patients with sickle β -thalassemia should be considered for hydroxyurea therapy.

Hemoglobin SC disease

The clinical course of Hb SC disease is extremely variable. Some patients are almost completely free of vaso-occlusive pain crises, while others have a clinical course that is indistinguishable from that of patients with homozygous sickle cell anemia. Only a small cohort of patients with Hb SC disease will fit the criteria used to select patients for hydroxyurea therapy. No controlled data exist on the efficacy of hydroxyurea in the treatment of Hb SC disease. Anecdotal experience at BWH and other institutions has been disappointing.

Hydroxyurea in Children

One of the most difficult issues with hydroxyurea is use in children. Only people 18 years and older were included in the MSH. Investigators and physicians are concerned about possible effects of hydroxyurea on growth and development in children since the drug blocks cells division. Although hydroxyurea is used at a lower dose in patients with sickle cell disease compared to other conditions (e.g., polycythemia vera), some suppression of cell growth almost certainly occurs.

Bone marrow transplants

Bone marrow transplants have proven to be effective in children.

- Trial period- Patients should remain on hydroxyurea for six to nine months before any decision is made on the efficacy of the treatment. The pattern of vaso-occlusive pain is sufficiently variable that cause-and-effect with hydroxyurea treatment of a single patient is difficult to assess. The infrequency of ACS means that even longer periods of assessment are necessary when treating this condition.

- Limiting effects

1. platelet count of less than 80,000.
2. neutrophil count (not white count) of less than 2,500
3. hemoglobin of less than 6 g/dl.
4. hair loss, GI upset, rash.

Monitoring hydroxyurea

5. hydroxyurea blood levels- Blood levels of hydroxyurea are difficult to interpret because of fluctuations that reflect, among other things, the pattern of drug use (e.g., once a day versus twice a day) and the timing of the blood test relative to ingestion of the HU.
6. MCV- The MCV rises in many patients treated with hydroxyurea. The response varies significantly between patients, making it unreliable as a measure of hydroxyurea efficacy or patient compliance with the drug.
7. Fetal hemoglobin levels- Fetal hemoglobin levels rise in many patients treated with hydroxyurea, but the response is variable. A correlation between patient clinical response and a rise in fetal hemoglobin levels has not been demonstrated.

- Contraindications to hydroxyurea Treatment

1. Pregnancy.
2. Poor or erratic follow-up.
3. allergies to hydroxyurea
4. Relative contraindications: - failure to use an accepted mechanism of birth control.