

**A COMPREHENSIVE UPDATED REVIEW ON CURRENT
MANAGEMENT OF SICKLE CELL ANEMIA****Karishma K. Bhange*, Vinod M. Thakre, Ujwala N. Mahajan and Pranali R. Gajbhiye**Dadasaheb Balpande College of Pharmacy, Near Swami Samarth Dham Mandir, Besa,
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Corresponding Author*Karishma K. Bhange**Dadasaheb Balpande
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Sickle cell infection (SCD) is an assortment of acquired blood problems that influence a considerable number of individuals in the U.S., especially African Americans. Individuals with SCD have an irregular sort of hemoglobin, Hb S, which polymerizes when deoxygenated, making the red platelets become deformed and inflexible. People with SCD are at higher danger of grimness and mortality from diseases, vaso-occlusive torment emergencies, intense chest disorder, and different confusions. Tending to the general wellbeing needs identified with SCD is a significant advance toward improving results and keeping up wellbeing for those influenced by the issue. Appropriate administration of sickle cell frailty (SCA) starts with setting up the right determination from the get-go throughout

everyday life, in a perfect world during the infant time frame. The distinguishing proof of influenced newborn children by neonatal screening programs permits early commencement of prophylactic penicillin and pneumococcal vaccinations, which help forestall overpowering sepsis. Continuous instruction of families advances the early acknowledgment of sickness delivered complexities, which permits quick and suitable clinical assessment and remedial intercession. Occasional assessment via prepared experts gives complete consideration, including transcranial Doppler assessments to distinguish kids in danger for essential stroke, in addition to appraisals for other parenchymal organ harm as patients become teenagers and grown-ups. Treatment moves toward that recently featured intense vaso-occlusive occasions are presently developing to the idea of preventive treatment.

KEYWORDS: Sickle cell anaemia, Classification, Pathophysiology, Genetics of Sickle cell anaemia, Inheritance, Management.

INTRODUCTION

Sickle-cell disease or sickle cell paleness is a deep rooted blood issue described by red platelets that expect an irregular, unbending, sickle shape. Typically, our red platelets are adaptable and round, which moving effectively through our vein. In sickle cell sickliness, the red platelets become unbending and tacky and are molded like sickle or bow moons. These unpredictably formed cells can stall out in little blood stream and oxygen to parts of the body. Sickling diminishes the cells, adaptability and results in a danger of different confusions. The sickling happens in view of a transformation in the hemoglobin quality. Future of 42 and 48 years for guys and females, separately.^[1,2]

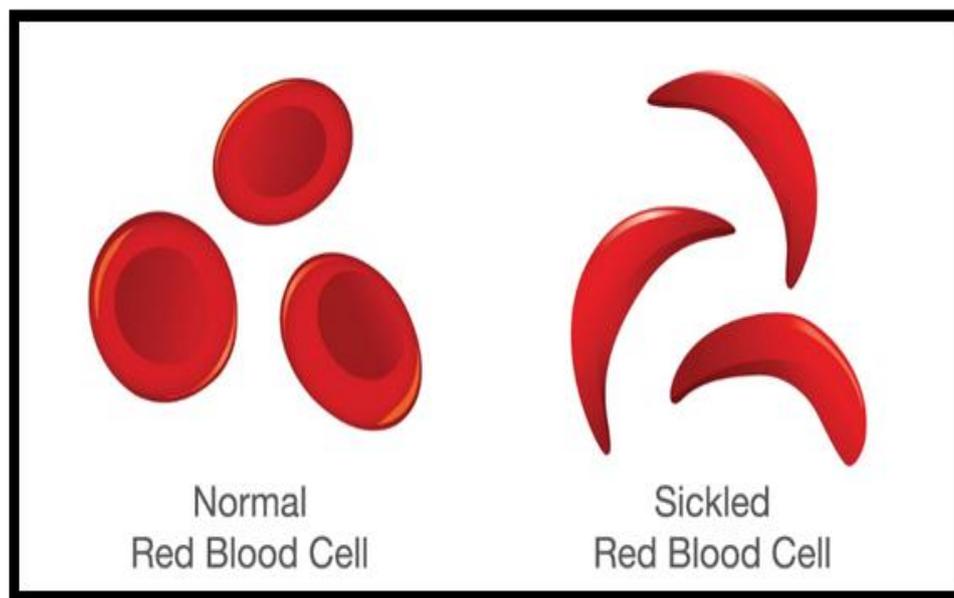


Fig. 1: Comparison of normal red blood cells and sickled red blood cells.

Hemoglobin S (HbS), the hemoglobin that is created because of this imperfection, is a hemoglobin tetramer ($\alpha_2/\beta_2 S_2$) that is inadequately solvent and polymerizes when deoxygenated.^[3] Overall, the rate of sickle cell infection surpasses that of most other genuine hereditary problems, including cystic fibrosis and hemophilia.^[4-5] It is seen worldwide however happens most as often as possible in Africans and less usually in those of Mediterranean, Latino, East Indian, and Arab descent.^[6] It is assessed that 16% of the populace in Africa has a sickle hemoglobinopathy which is the most elevated extent around the world. The Americas and the East Mediterranean district speak to the following most

noteworthy extent of sickle cell hemoglobinopathy as outlined by the World Health Organization. SCD results from any mix of the sickle cell quality with some other irregular β -globin quality and there are numerous kinds of SCD. The most widely recognized sorts incorporate sickle cell paleness (Hb SS), the sickle beta-thalassemias (Hb S β 0 and Hb S β +), hemoglobin SC sickness (Hb SC) and sickle cell infection with genetic constancy of fetal hemoglobin (S/HPFH). HbSS is the most well-known type of sickle cell infection. Patients with Hb SS and Hb S β 0, by and large, have the most extreme types of SCD including lower hemoglobin levels and more successive vasoocclusive and hemolytic entanglements. Sickle-C (Hb SC) illness is the second most basic type of SCD. Patients with this sort of SCD for the most part have a more considerate clinical course than do patients with Hb SS or sickle β 0 - thalassemia. Similarly, patients with Sickle β + - thalassemia and S/HPFH likewise by and large have a more kindhearted clinical course and patients with S/HPFH may really have hemoglobin levels that are or approach typical. Grown-ups with sickle cell sickness who live in the United States have a diminished future with the chances of making due past the seventh decade of life answered to be under 30%.^[7] Historically, Platt et al. revealed an enormous number of grown-ups with sickle cell sickness who kicked the bucket during intense sickle cell related intricacies, for example, torment, intense chest disorder, and stroke. In this period, the most well-known reasons for death in grown-ups from sickle cell sickness revealed are pneumonic hypertension, abrupt passing of obscure etiology, renal disappointment, and infection.^[8] concerning youngsters with SCD, in the created world, the death rate is assessed to be as low as 0.5-1.0 per 100,000 kids. This is as opposed to higher rates in agricultural nations, for example, the Republic of Benin which as of late revealed a death pace of 15.5 per 1,000 kids (or 1,550 for every 100,000 children).^[9] The most well-known reasons for death in youth from sickle cell illness are contamination, intense chest disorder and stroke.^[10-11]

Classification of sickle cell disease

Sickle cell iron deficiency is the name of a particular type of sickle cell infection in which there is homozygosity for the change that causes HbS. Sickle cell weakness, is additionally alluded to as "HbSS", "SS illness", "hemoglobin S" or changes thereof. In heterozygous individuals, just 1 sickle quality and one typical grown-up hemoglobin quality, it is alluded to as "HbAS" or sickle cell characteristic. Other more uncommon structures sickness incorporate sickle hemoglobin C illness (HbSC), sickle beta - in addition to thalassemia (Hbs/B) and sickle beta - zero – thalassemia (Hbs/P). These different types of sickle cell sickness are compound heterozygeous states in which the individual has just one duplicate of

another anomalous hemoglobin allele. The expression "infection" is applied since the acquired anomaly causes a neurotic condition that can prompt demise and serious confusions. Not all acquired variations of hemoglobin are adverse, an idea known as hereditary polymorphism.^[12]

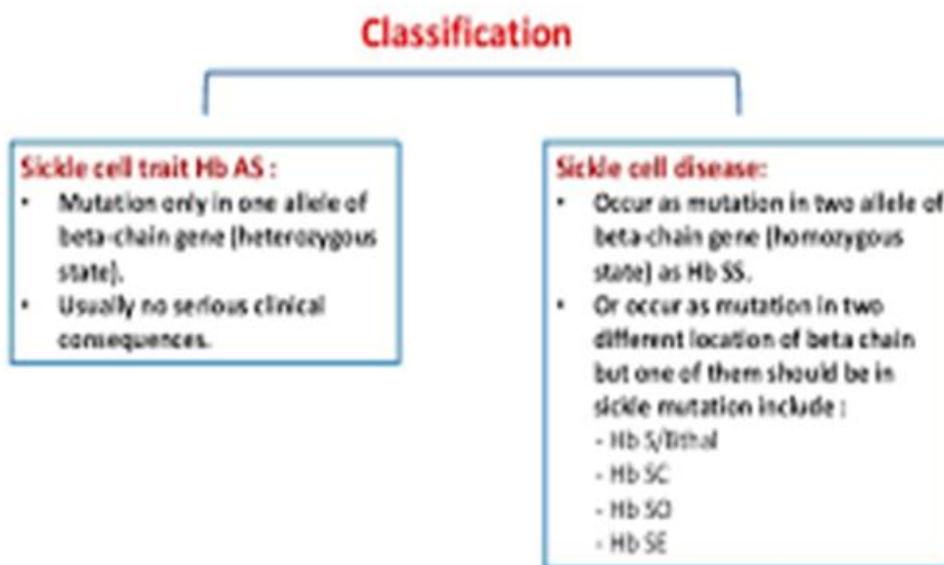


Fig. 2: Classification of sickle cell disease.

Pathophysiology

Sickle cell frailty is a solitary quality problem which is created by a transformation in the beta globin quality which is found on chromosome. This prompts substitution of glutamic corrosive (a hydrophilic amino corrosive) in the 6th situation with valine (a hydrophobic amino corrosive). Hemoglobin S is shaped from the relationship of two α -globin subunits with two freak β globin subunits.^[13] On introduction to hypoxic conditions, the nonattendance of a polar amino corrosive at position six of the β -globin chain supports the non-covalent polymerization (total) of hemoglobin, which changes the shape and flexibility of RBCs. In low oxygen media, the cells accomplish an unusual shape which isn't versatile.^[14] At the point when ordinary oxygen pressure is recaptured, the cells neglect to re-visitation of their typical shape. In this way, these mutilated RBCs can't go through restricted vessels, prompting impediment of veins. Vaso-impediment brings about hand-foot disorder in kids. Moreover, contaminations, stroke, and intense chest torment are a portion of the significant inconveniences. The vast majority of these entanglements start in early life, yet become more clear with propelling age. Diseases, parchedness, chilly climate, and stress are considered as encouraging variables for these confusions. Therapies of SCD are generally coordinated

toward avoidance of or diminishing sickling and hence decreasing the frequency of vascular impediment. The anomalous state of the RBCs prompts their decimation by hemolysis. A compensatory bone marrow hyperplasia can't coordinate the pace of RBC demolition. Sickle cells just endure 10–20 days in contrast with ordinary RBCs which regularly live 90–120 days.^[15]

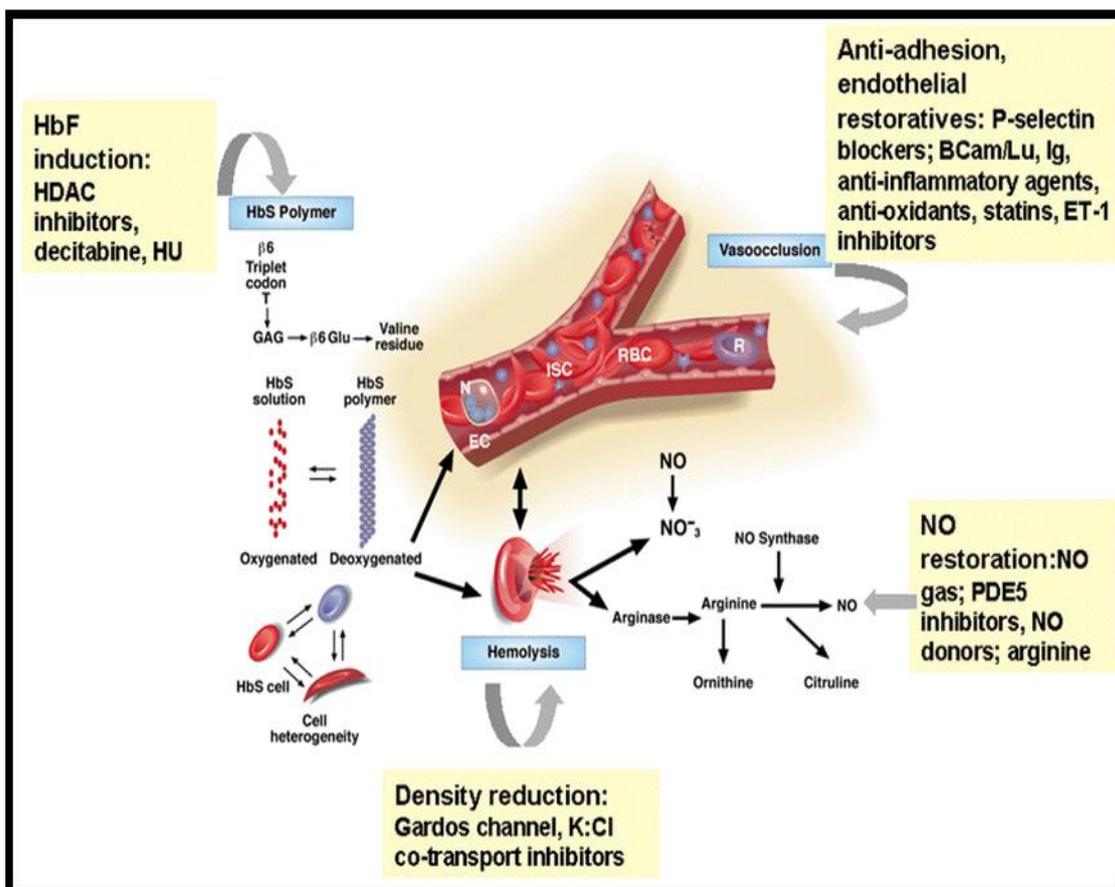


Fig. 3: Pathophysiology of sickle cell anemia.

Genetics of sickle cell disease

The possibility in cell structure emerges from an adjustment in the structure of hemoglobin. A solitary change in an amino corrosive makes hemoglobin total sickle cell pallor is acquired in an autosomal latent example, which implies that the two duplicates of the quality in every cell have transformations. The guardians of a person with an autosomal latent condition each convey one duplicate of the changed quality, yet they normally don't give indication and manifestations of the condition.^[16]

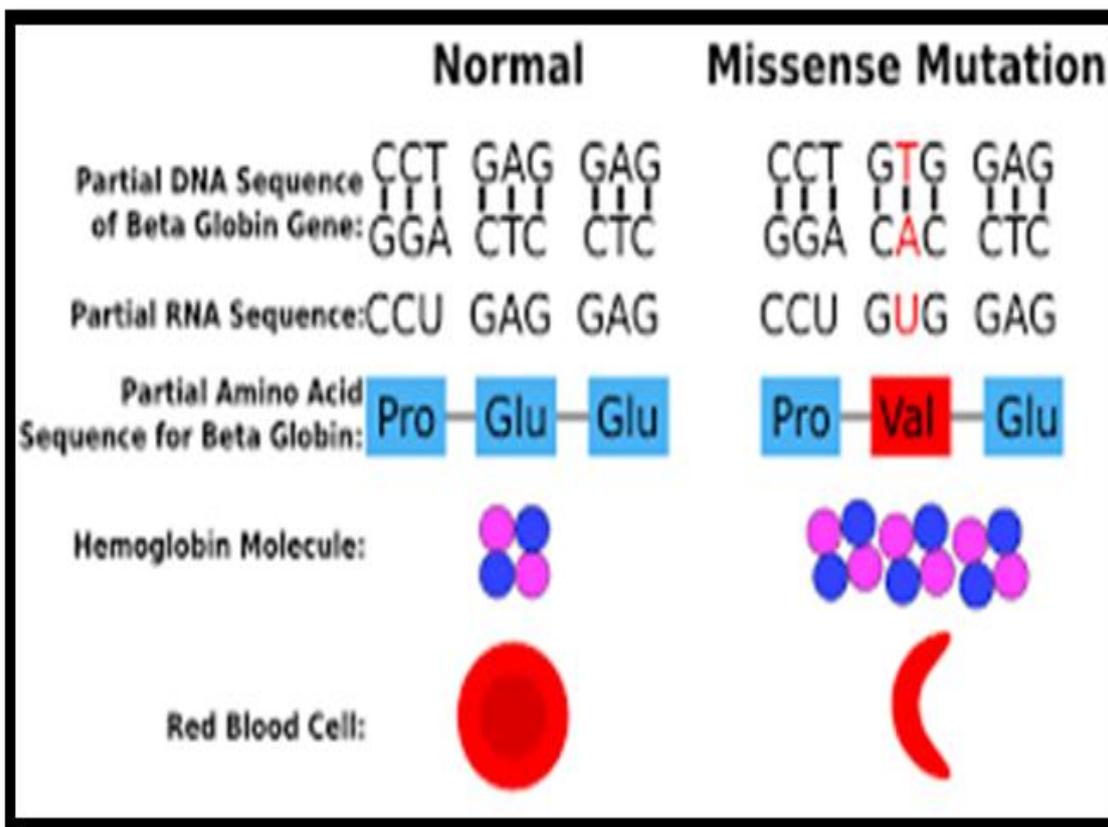
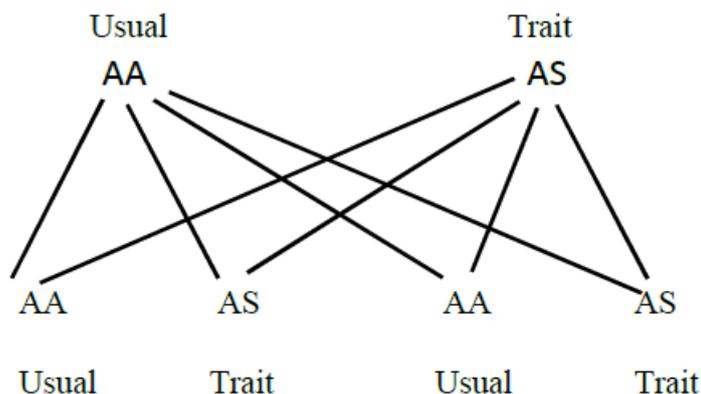


Fig. 4: Genetics of sickle cell disease.

Inheritance of sickle cell disease^[17,18]

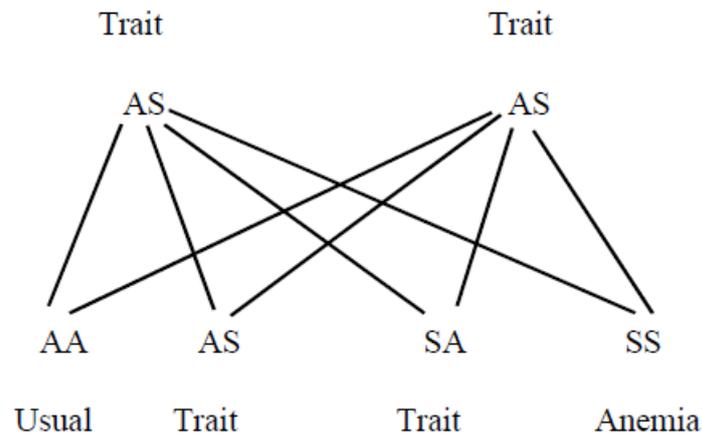
Case-1

- If one parents has sickle cell trait (HbAS) and the other does not carry the sickle hemoglobin at all (HbAA) then none of the children will have sickle cell anemia.
- There is a one in two (50%) chance that any given child will get one copy of the HbAS gene and therefore have the sickle cell trait.
- It is equally likely that any given child will get two HbAA genes and be completely unaffected.

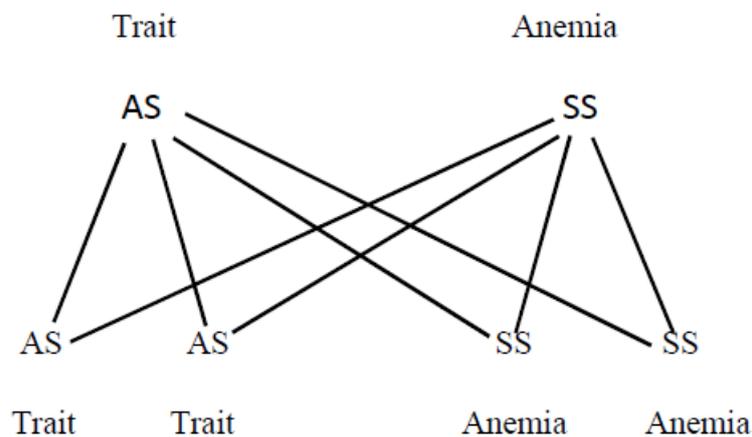


Case-2

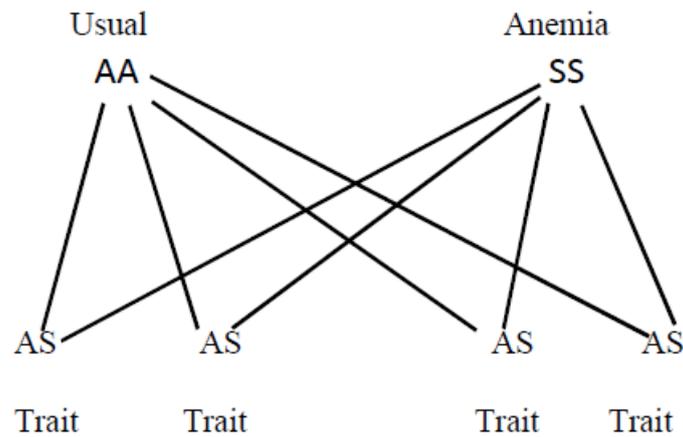
- If both parents have sickle cell trait (HbAS) there is a one in four (25%) chance that any given child could be born with sickle cell anemia.
- There is also a one in four chance that any given child could be completely unaffected.
- There is a one in two (50%) chance that any given child will get the sickle cell trait.

**Case-3**

- If one parent has sickle cell trait (HbAS) and the other has sickle cell anemia (HbSS) there is a one in two (50%) chance that any given child will get sickle cell trait and a one in two (50%) chance that any given child will get sickle cell anemia.
- Two offspring are affected with sickle cell anemia.

**Case-4**

- If one parent has sickle cell anemia (HbSS) and the other is completely unaffected (HbAA) then all the children will have sickle cell trait.
- None will have sickle cell anemia. (No Affected any offspring)



Complications

Sickle cell anemia can lead to a host of complications, includes are as follows

Stroke: A stroke can happen if sickle cells block blood stream to a region of mind. Sing of stroke incorporate seizures, shortcoming or deadness of arms and legs, unexpected discourse challenges, and loss of awareness. On the off chance that infant or youngster has any of these signs and side effects, look for clinical treatment right away.^[19]

Intense chest disorder: This perilous entanglement causes chest torment, fever and trouble in relaxing. Intense chest disorder can be brought about by a lung contamination or by sickle cells impeding veins in lungs. It may require crisis clinical treatment with anti-microbials and different medicines.^[20]

Pneumonic hypertension: People with sickle cell paleness can grow hypertension in their lungs (Pulmonary hypertension). This intricacy typically influences grown-ups instead of kids. Windedness and exhaustion are basic indications of this condition, which can be deadly.^[21]

Organ harm: Sickle cells that square blood course through veins promptly deny the influenced organ of blood and oxygen. In sickle cell pallor, blood is additionally persistently low on oxygen. Constant deprivation of oxygen rich blood can nerves and organs in body, incorporate kidneys, liver and spleen. Oragan harm can be lethal.^[22]

Visual deficiency: Sickle cells can impede small veins that supply our eyes. Additional time, this can harm the segment of the eye that measures visual pictures (Retina) and lead to visual impairment.^[23]

Gallstones: The breakdown of red platelets creates a substance called bilirubin. A significant level of bilirubin in our body lead to gallstones.^[22]

Diagnosis

Sickle cell pallor is recommended when the unusual sickle formed cells in the blood are distinguished under a magnifying lens. Testing is commonly performed on a smear of blood utilizing an extraordinary low – oxygen planning. This is alluded to as a sickle prep. Other prep tests can likewise be utilized to distinguish the strange hemoglobin S, including solvency tests performed on containers of blood arrangements. The infection can be affirmed by explicitly measuring the sorts of hemoglobin present utilizing a hemoglobin electrophoresis.^[24]

Parental diagnosis (before birth)

Parental determination of sickle cell frailty is conceivable utilizing amniocentesis or chorionic villus inspecting. The example acquired is then tried for DNA investigation of the fetal cells. The hemoglobin electrophoresis test definitely recognizes the hemoglobins in the blood by isolating them. The partition of the diverse hemoglobin is conceivable in view of the special electrical charges they each have on their protein surfaces, causing them each to move distinctively in an electrical field as tried in the research center.^[23]

A blood test can check for hemoglobin

The inadequate type of hemoglobin that underlies sickle cell paleness. In the United States, this blood test is important for routine infant screening done at the medical clinic. Be that as it may, more established kids and grown-ups can be tried, as well.

In grown-ups, a blood test is drawn from a vein in the arm. In small kids and children the blood test is typically gathered from a finger or heel.

On the off chance that the screening test is negative, there is no sickle cell quality present.

In the event that the screening test is positive, further tests will be done to decide if a couple of sickle cell qualities are available.

Checking for a low red platelet tally (pallor) will be finished.^[25]

Hereditary advising^[26]

Two tests can be utilized to help eager guardians see whether their kid is influenced.

1) Amniocentesis

Amniocentesis, done for the most part at 14-16 months of pregnancy, tests an example of the amniotic liquid in the belly for hereditary deformities (the liquid and the hatchling have a

similar DNA). Under nearby sedation, a slim needle is embedded through the lady's mid-region and into the belly. Around 20 millilitres of liquid (approximately 4 teaspoons) is removed and shipped off a lab for assessment. Test outcomes regularly take 1 fourteen days.

2) Chorionic Villus testing or CVS

CVS, includes the evacuation and testing of a tiny example of the placenta during early pregnancy. The example, which contains a similar DNA as the embryo, is taken out by catheter or a fine needle embedded through the cervix or by a fine needle embedded through the midsection. The tissue is testicles for hereditary changes distinguished in an influenced relative. Results are normally accessible inside about fourteen days.

Management of sickle cell anemia

The executives of sickle cell iron deficiency is normally pointed toward keeping away from torment scenes, assuaging manifestations and forestalling difficulties. Medicines may incorporate meds and blood bondings. For certain youngsters and young people, an undeveloped cell relocate may fix the illness.^[27]

Emergencies the executives is typically strong except if blood bonding is demonstrated. The point of therapy is to forestall the sickling of RBCs, lack of hydration, hypoxia, and acidosis that can prompt sickling. Difficult assault is the principle introduction. Subcutaneous morphine or another solid narcotic is as often as possible needed for the executives of extreme assaults of torment. Pethidine can accelerate Grand mal seizures; in this manner, it is desirable over be dodged. Good liquid admission is required.^[28]

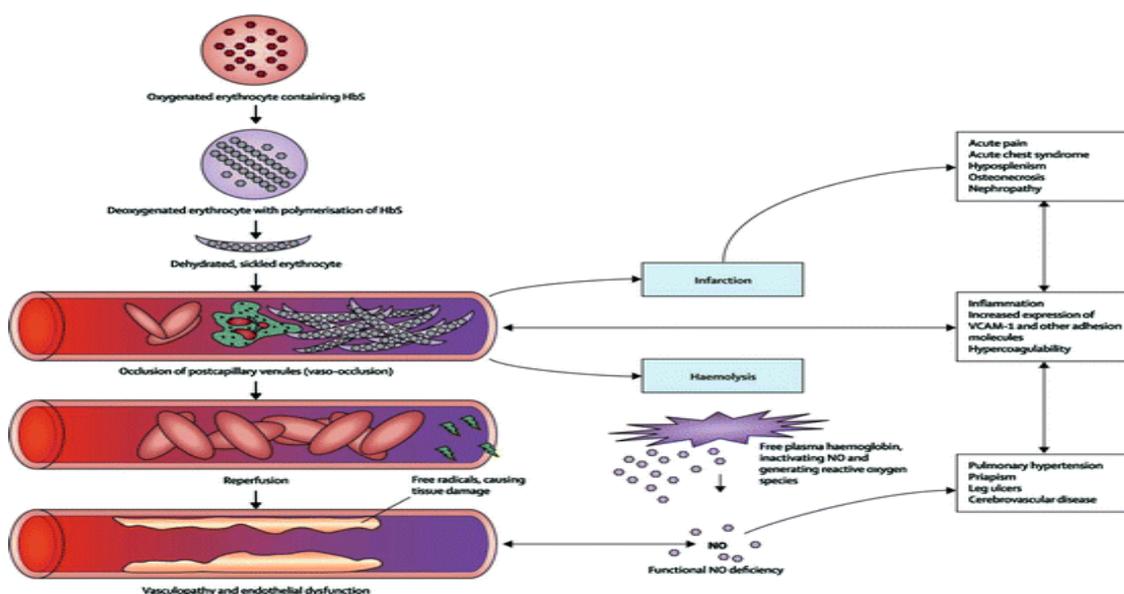


Fig. 5: Management of sickle cell anemia.

1. Folic Acid and Penicillin

Kids brought into the world with sickle-cell illness will take folic corrosive (1 mg portion) day by day forever. Also, Patients from birth to five years old need to take penicillin day by day because of weakness to pneumococcal disease.^[29]

2. Nitric oxide

Individuals with sickle cell weakness have low degrees of nitric oxide in their blood. Nitric oxide of nitric oxide in their blood. Nitric oxide is a gas that assists keep with bleeding vessels open and diminishes the tenacity of red platelets. Therapy with breathed in nitric oxide may keep sickle cells from clustering together.^[30]

3. Intense chest condition

Intense chest condition is an intense disease with fever as well as respiratory side effects related with another lung penetrate. It is the fundamental driver of mortality in grown-ups with SCD and the most well-known reason for emergency unit. The patient who needs mechanical ventilation is accounted for to have a death pace of 5%. Side effects incorporate hack, wheeze, dyspnea, and chest torment, which might be pleuritic or influence the ribs and sternum. The intense chest condition is special to SCD and is related with a more serious course and more regrettable result than pneumonia. Blood bonding is utilized to treat patients with intense chest disorder and will improve the oxygenation. Blood bonding is valuable in less extreme cases with a low Hb notwithstanding, trade bonding is required in serious cases, in patients with high Hb levels, or those with serious hypoxia. The objective is a last Hb level of 9–10 g/dL. Extreme hypoxia, dyspnea and respiratory acidosis are signs for starting progressed respiratory help.^[31]

4. Stroke

Patients with SCD are usually connected with ischemic and hemorrhagic strokes, with a pervasiveness pace of over 5%. Rate of stroke is significantly decreased after the presentation of transcranial Doppler screening and essential stroke avoidance with bonding. A stroke might be hastened by drying out or a correspondent disease. Early imaging is basic to affirm the analysis and prohibit discharge. X-ray is the imaging of decision with high affectability and explicitness. In the event that the MRI affirms a stroke, prompt trade bonding should be done to accomplish a HbS under 30%. Ischemic stroke avoidance should be possible by long haul trade bonding, anyway the viability of antiplatelet treatment in essential or optional stroke counteraction in SCD isn't demonstrated.^[32]

5. Sepsis

Patients with sickle cell pallor have utilitarian hyposplenism. This makes them more vulnerable to disease by capsulated life forms. Sepsis brought about by gram-negative living beings is basic along with osteomyelitis. Kids with sickle cell paleness must be inoculated against pneumococcal, meningococcal, and Hemophilus flu disease. Oral penicillin could be given on regular routine after the hour of analysis to prepare for pneumococcal disease.^[30]

6. Different intricacies of SCD

Patients with SCD have low renal concentrating capacity and are hence helpless to drying out. Over the long run, the patients may show proteinuria and persistent renal disability as Sickle Cell Disease (SCD) an aftereffect of glomerular harm. This leaves patients obligated to intense kidney injury during an emergency. Constant lung sickness is normal and shows as either a prohibitive lung imperfection or an overnight hypoxia and rest apnea. Aspiratory hypertension is more normal in SCD and can prompt checked hypoxia.

6.1. Admission to basic consideration unit

Patients with sickle cell paleness may require admission to the emergency unit because of liver cell disappointment, sepsis, or multi-organ harm. This intense decay may require dire blood bonding focusing on a Hb of 9–10 g/dL and HbS% of under 30%. This will improve tissue oxygenation and perfusion, whatever the fundamental etiology.

6.2. Bonding in SCD patients

Standard blood bonding is expected to forestall cerebrum strokes. Unique circumstances, for example, circulatory unsettling influences, sequestration emergencies and priapism may require blood bonding to upgrade oxygen transport. Fractional trade bonding is generally wanted to basic bonding if standard or numerous bondings are essential. It diminishes the iron over-burden and forestalls expanded blood consistency. In a red platelet bonding, red platelets are eliminated from a stockpile of gave blood, at that point offered intravenously to an individual with sickle cell sickliness. Blood bondings increment the quantity of typical red platelets available for use, assisting with calming weakness. In youngsters with sickle cell iron deficiency at high danger of stroke normal blood bondings can diminish the danger. Bonding can likewise be utilized to treat different entanglements of sickle cell frailty, or they can be given to forestall complexities. Blood bondings convey some danger, remembering contamination and abundance iron development for body. Since overabundance iron can harm heart, liver and other bonding may require treatment to diminish iron levels.^[30]

6.3. Bone marrow transplant

Bone marrow transplant, otherwise called immature microorganism transplant, offers the solitary possible remedy for sickle cell anemia. It is generally reserved for individuals more youthful than age 16 on the grounds that the dangers increment for individuals more seasoned than 16. Finding a benefactor is troublesome, and the methodology has genuine dangers related with it, including demise.

A bone marrow transplant includes supplanting bone marrow influenced by sickle cell anemia with sound bone marrow from a giver. The method for the most part utilizes a coordinated benefactor, for example, a kin, who doesn't have sickle cell frailty. For some, benefactors aren't accessible. In any case, foundational microorganisms from umbilical string blood may be a choice.

Due to the dangers related with a bone marrow transplant, the methodology is suggested distinctly for individuals, typically youngsters, who have huge indications and issues from sickle cell pallor.^[34]

On the off chance that a benefactor is discovered, the individual with sickle cell sickness gets radiation or chemotherapy to devastate decrease their bone marrow undifferentiated organisms. Solid undifferentiated organism from the benefactor are infused intravenously into the circulatory system of the individual with sickle cell sickness, where they move deep down marrow and start producing fresh blood cells.

The maker requires an extensive emergency clinic remain. After the transfers, you'll get medications to help forestall dismissal of the gave undeveloped cells. All things being equal, your body may dismiss the transfer, prompting dangerous entanglement.^[35]

7. Experimental treatment

Scientists are studying new treatments for sickle cell anemia, including:

7.1. Quality treatment

Specialists are investigating whether embeddings an ordinary quality into the bone marrow of individuals with sickle cell frailty will bring about typical hemoglobin. Researchers are additionally investigating the chance of killing the imperfect quality while responding another quality liable for the creation of fetal hemoglobin – a sort of hemoglobin found in

babies that keeps sickle cells from framing. Possible medicines, utilizing quality treatment are far off, be that as it may.

- Scaling up strategy to different patients is a nontrivial challenge.
- Safety and productivity must be set up via cautious clinical preliminaries with broadened understanding follow – up.
- Gene designing techniques are quickly involving and ought to encourage improvement of "second era" quality treatment approaches in the coming years. After numerous long stretches of preclinical research facility examination, quality treatment alternatives are presently not too far off for patients with Sickle cell sickness.
- Although a few of the underlying obstacle to sickle cell sickness quality treatment seem to have been survived, it is reasonable to perceive boundaries that remain.^[32]

CONCLUSION

Sickle cell anemia is a homozygous type of HbS (HbSS). This outcome from single point substitution of glutamine by valine at position 6 of β -globin chain. This diminishes solubility of the red cells which thusly prompts polymerisation and vaso-occlusion in the vasculature. The relationship of two freak β - globin subunits structures hemoglobin S (HbS). Under low - oxygen conditions, the nonappearance of a polar amino corrosive at position of six of the β - globin chain advances the non - covalent polymerization of hemoglobin, which twists red platelets into a sickle shape and diminishes their versatility. It will be relevant to have who listic care for those influenced. Incredible advances have been made in the administration of SCD yet huge numbers of these are costly and reliant on clinical foundation, which may set aside a long effort to creating asset helpless high-hazard social orders. Without a doubt, not many SCD patients have been effectively treated with hematopoietic undifferentiated cell transplantation and, quality treatment has not been fruitful yet in restoring SCD. Going ahead, consideration should zero in on the consideration and the board of youngsters and grown-ups with SCA, and address personal satisfaction just as unexpected issues. More forceful treatment of SCA is upheld by current proof, and remedial alternatives with hydroxyurea should be viewed as right off the bat throughout everyday life.

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