A Genetic Disorder: Sickle Cell Anaemia & it's Cure

Miss. Chetna Dhande[1], Miss Shivani Mahalle[2], Miss Pranjali Kshirsagar[3], Dr. Atul Hemke[4], Dr. Milind Umekar[5] , Mulla M[6]

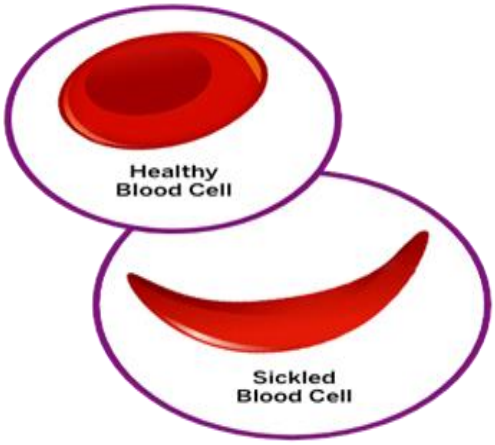
[1,2,3,4,5,6]*Smt. Kishoritai Bhoyar College of pharmacy, Kamptee Dist. Nagpure, pin 441002*

Abstract: Sickle cell is a homozygous form of HbS (HbSS). Due to single base pair point mutation in the β globin gene resulting in the substitution of the amino acid valine for glutamic acid in the β globin chain. The β globin gene is found on the short arm of chromosome 11. The association of two mutant β globin subunits form hemoglobin S (Hbs). Under low oxygen condition, the absence of a polar amino acid at the position of six of the β globin chain promotes the non-covalent polymerization of hemoglobin, which distorts red blood cells into cell sickle shape and decrease their elasticity. In sickle cell disease low oxygen tension promotes red blood cell sickling and repeated episodes of sickling damage the cell restored. The Actual anemia of the illness is caused by hemolysis the destruction of the red cell inside the spleen. Those suffering from this illness are present with chronic anaemia which those with normal adult haemoglobin genotype will not survive because of the misshape of the cells leading to the destruction of the cell at the spleen.

SICKLE CELL DISEASE INTRODUCTION

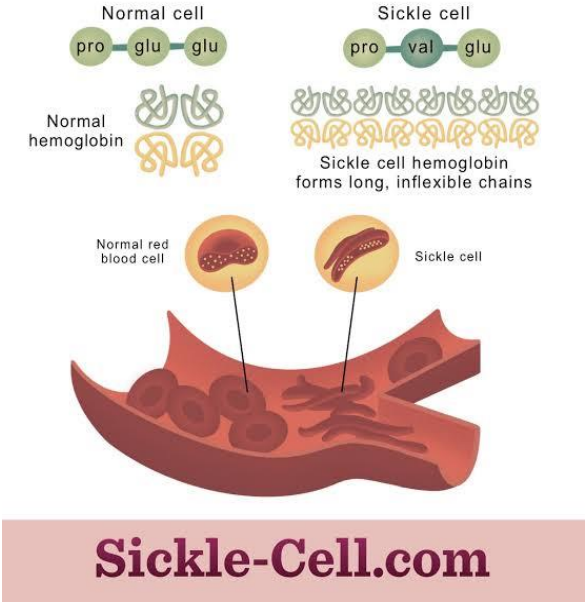
Sickle cell anemia is a homozygous form of HbS (HbSS). Sickle cell disease or sickle cell anemia is a lifelong disorder. Red blood cell assumes an abnormal, rigid, sickle shape.(1st .). Sickle shape cells occur because of mutation in the hemoglobin gene or due to a single base pair point mutation in the β-globin gene resulting in the substitution of the amino acid valine for glutamic acid in the β globin chain of hemoglobin referred to as hemoglobin S [Hbs](2). The life expectancy of 42 to 48 years for males and females. In sickle cell disease, low oxygen tension promotes red blood cell sickling and reported episodes of sickling damage the cell restore.

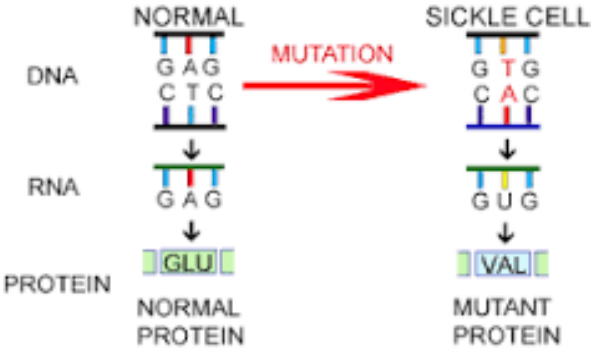
Due to abnormal acids acid in the β-globin chain, HbS forms long, insoluble polymers when deoxygenated, and the red blood cells (RBCs) containing HbS become less deformable and form a "sickle" shape (3). Sickle cell disease stems from an abnormality of the RBC, it is essentially a multisystem disorder, affecting almost every organ system of the body.



PATHOPHYSIOLOGY OF SICKLE CELL

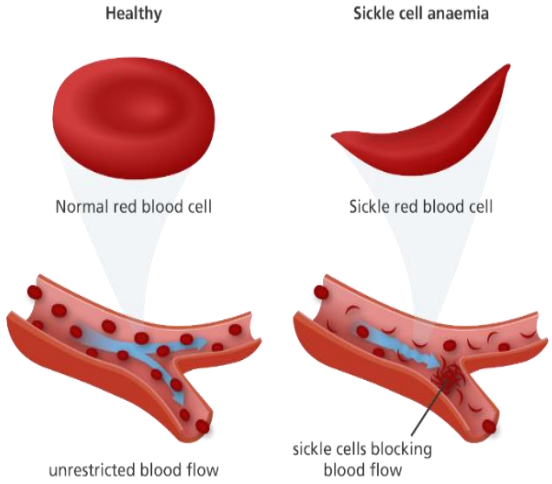
Sickle cell anemia is caused by a point mutation in the β globin chain of hemoglobin causing the amino acid, glutamic acid to be replaced with the hydrophobic amino acid valine at 6th position. (1)





The loss of red blood cell elasticity is central to the pathophysiology of sickle cell disease. Normal red blood cells are quite elastic, which allows the cells to deform to pass through capillaries.(1)

Under low oxygen condition absence pf polar amino acid at β globin chain promote the non-covalent polymerization of hemoglobin which reptaured the RBC in a sickle shape and decrease its elasticity. In sickle cell disease due to low oxygen, it promotes the red blood cell sickling shape and reports its cycle of sickling and damages the cells. Sickle cells and raptured cell block the blood flow.



Due to low oxygen tension sickle cells may survive just for 10 to 20 days. Normal red blood cells have half a life are 100 days. The destruction of the red cells inside the spleen because of the misshape of sickle cell.(1,4)

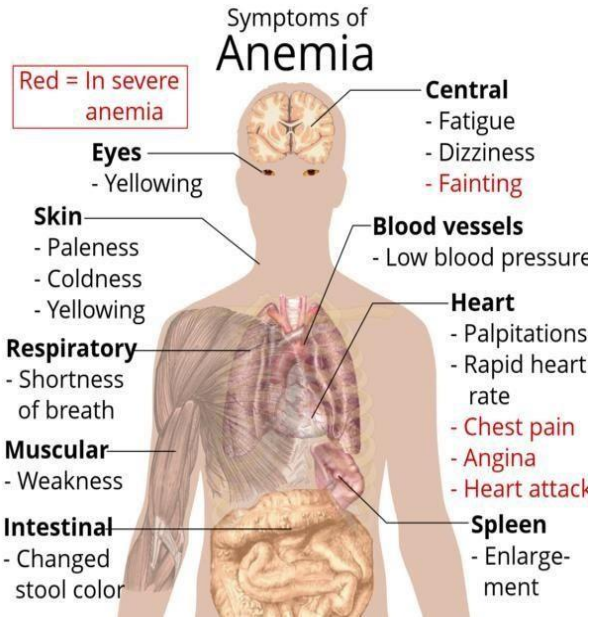
SIGNS AND SYMPTOMS

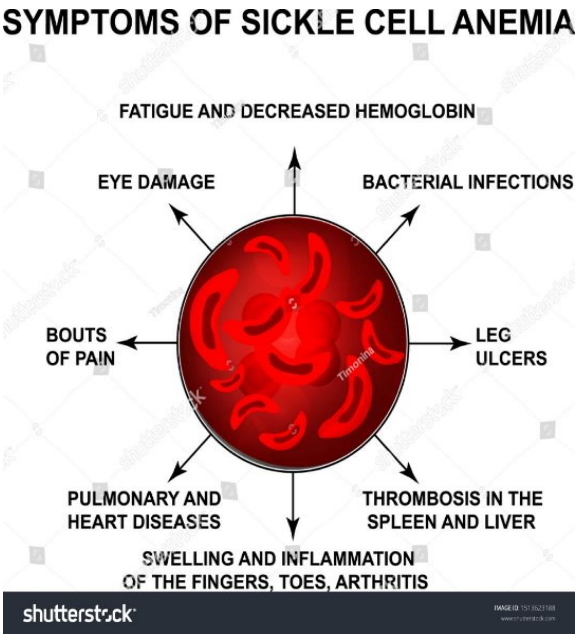
Sickle cell disease may lead to various acute and chronic complications, several of which are potentially lethal. Vaso occlusive crisis.

The Vaso occlusive crisis is caused by sickle-shaped red blood cells that obstruct capillaries and restrict blood flow to an organ, resulting in ischemia, pain, and often organ damage.

1] Vaso occlusive Crisis: Pain Crisis, Body pain, Cheats pain, Joint pain

2] Weakness, Fever, Yellowish eyes





Vaso-Occlusive Crisis

The vaso -occlusive crisis is caused by sickle-shaped red blood cell that obstructs capillaries and restricts

blood flow to an organ, resulting in ischemia, pain, and often organ damage[1]. The frequency, severity, and duration of these crises vary considerably.

An acute episode of pain is also commonly referred to as a sickle cell pain crisis or vaso-occlusive[5,6]. Acute chest syndrome is the most common predictor of death in patients with SCD or Hospitalization.[5,7]

Painful crises, considered the hallmark of SCD, are defined as serve pain lasting for 2 or more hours that is attributed to SCD. The sites that are normally affected include the arms, legs, back, abdomen, chest, and head. It is the most common cause of hospitalization and frequent pain is associated with poor quality of life and increased risk of death[3,8].

In Vaso-occlusive crisis, the most common causes of hospitalization and frequent pain (define as 2 or more painful events year for three years) is associated with poor quality of life and increased risk of death. The average hospital stay is approximately 9-11 days in adult.

Polymerization

Polymerization of deoxygenated sickle cell hemoglobin leads to decreased deformability of RBCs and is responsible for the characterizes "Sickle" shape of RBCs in patient with SCD. Sickle RBCs are rigid and do not easily flow through the microcirculation; they can obstruct the vasculature, resulting in pain episodes and end-organ injury[5].

Acute Painful Episode

An Episode of acute pain generally called as "Sickle cell Crisis" by Diggs, who used the expression "Crisis" to refer to any new rapidly developing syndrome in the life of a patient with sickle cell disease.

Acute pain symptoms are joint pain, bone pain, and acute chest syndrome in these all pain episodes is approximately 7-14 days. Acute pain is the first symptom of the disease is more than one-fourth of patients, the most frequent symptom after age 2 years[9], and the complication for which patients with sickle cell disease most commonly seek medical attention[10].

Acute Chest Syndrome

Acute Chest Syndrome (ACS) is a frequent complication of sickle cell disease with a frequency second only to the painful crisis[11,12]. Patient with sickle cell disease can present with acute chest syndrome, or it may develop sometimes after onst of sever pain. Therefore awareness should be maintained through out hospital admission. This syndrome is defined as the development of a new radiodensity on chest radiography accompanied by fever and/or respiratory Symptoms[13]. Due to low oxygen or blocked blood flow, the respiratory or acute chest pain occurs. Symptoms and signs of acute pain, less commonly abdominal pain, fever, tachypnea, leucocytosis and a pulmonary infiltrate on the chest radiography.

The major danger of the acute chest syndrome is hypoxemia and its attendant wide spread sideling and vaso-occlusion, which create a risk of multi-organ failure.

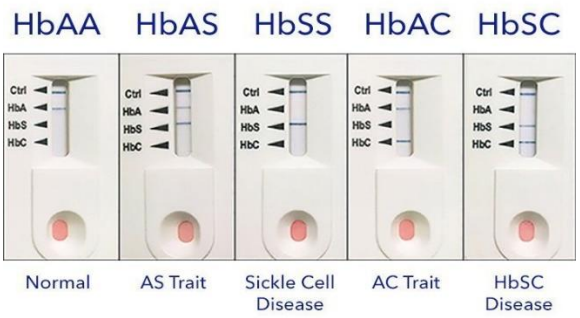
Diagnosis of Sickle Cell

In Hbss the fall blood count (FBC) reveals hemoglobin level in the range of 6-8g/dl with a high reticulocyte count. In other forms of sickle cell disease, Hb levels tend to be higher.

Sickling of the red blood cells, on a blood film, can be induced by the addition of sodium metabisulfite. The presence of sickle hemoglobin can also be demonstrated with the "Sickle Solubility test". A mixture of hemoglobin (Hbs) in a reducing solution (such as sodium dithionite) gives a turbid appearance, where as normal Hb gives a clear solution. Abnormal hemoglobin form can be detected on hemoglobin electrophoresis, a for, of gel electrophoresis on which a various types of hemoglobin move at varying speeds. HbSS and HbSc can be identified here.

The diagnosis can be confirmed with high performance liquid chromatography (HPLC).

Traditional methods employed in the diagnosis of SCA involved the use of Hemoglobin Electrophoresis and High-Performance Liquid Chromatography(HPLC). HPLC is an automated technique and hence is less laborious. Gradually focus shifted to Isoelectric Focusing (IEF) which offers a higher resolution and is more cost-effective. However, HPLC has the ability to differentiate between different Hb variants and hence is more reliable.



Management of Sickle cell

A] Nutrition:

Sickle cell patients have increased metabolism rate and protein turnover which is balanced by high-calorie intake. Folic acid requirements are increased by hemolysis above the normal level of 50g/day and as much as 500ng daily has been necessary to reverse established megaloblastic change[14]. Red blood cells are rich in zinc. Omega-3 fatty acids have been purified from fish oil and tested for benefits as antioxidant, antithrombotic, and anti-inflammatory benefits. The clinical trail has used products with different purity, different properties of types of omega-3 fatty acids, and different dosages[15].

B] Prophylaxis against infection

Regular immunization against the common viral and bacterial infections of childhood is especially important and diligence is necessary to ensure that vaccine schedules are completed. Tetanus toxoid "booster" should be given at regular intervals because of the prevalence of leg ulceration. Prophylactic penculin is essential in early childhood to prevent pneumococcal septicemia.

C] Avoidance Of Adverse Climatic Conditions

The commonest precipitating factor for the painful crisis is cold and proper clothing many minimize its effects so that patients understand the importance of cold and keeping warm at the cold wet periods of the year and at night.

D] Hydration

Dehydration and hemo concentration are known to precipitate a painful crisis in some patients. The maintenance of adequate hydration is very important where febrile conditions increase fluid loss, especially in countries with high ambient temperatures.

Therapeutic agents that may modify acute vaso-occlusive crisis

The FDA has approved l-glutamine and crizanlizumab for SCD to reduce the frequency of VOC, they are not for treating VOC in the acute setting to prevent the development of sVOC. To be beneficial in treating VOC, an agent has to be able to mediate its effects promptly after administration to interrupt the vicious cycle of VOC to prevent VOC. Clinical trials investigating specific agents for treating VOC have focused on targeting the downstream events and have uniformly been disappointing. This is not surprising taking into consideration that VOC is a complex pathologic process and leads to many downstream events.

Currently, the mainstay of management in SCD patients with acute VOC is intravenous hydration and opioid analgesia. This conservative approach aims to treat the patients symptomatically and wait for the VOC process to resolve spontaneously. In this section, we will discuss some of the therapeutic agents that may be investigated for use during acute VOC to either protect erythrocytes that are not already involved in the hemoglobin polymerization process from undergoing sickling or downregulate the downstream effects of VOC[16].

Anti-inflammatory Agents

Anti-inflammatory agents may prevent the development of VOC. Although NSAID such as ketorolac has been incorporated in the pain management of SCD[17]. Since intense inflammatory processes are associated with the VOC. For treating SCD, less than 30% of SCD patients are on long term hydroxyurea[18]. Therefore a high proportion of SCD patients admitted to the hospital are not already on the medication. Its use during active VOC will not in induction on HbF. However, hydroxyurea mediates anti-inflammatory processes associated with Sickle cell disease, via regular use of hydroxyurea and may prevent the development of VOC.

Sickle cell Disease: Pharmacotherapy (Disease Modifier)

HYDROXYUREA:

Hydroxyurea oral capsule is available as the brand-name drugs Hydrea and Droxia. Hydrea is also available as a generic drug.

Hydroxyurea represents the only major breakthrough in the pharmacotherapy of sickle cell disease and it is the only drug that is approved by the U.S., Food and Drug Administration (FDA) For the treatment of adults with sickle cell disease[19] .

Hydroxyurea works is by increasing the amount of fetal hemoglobin and therefore decreasing the amount of sickle hemoglobin, higher fetal hemoglobin level improved the shape and function of the red blood cells maysof a complication in sickle cell disease caused by blocked blood vessels.

Treatment with hydroxyurea has not only been shown to significantly decrease the incidence of painful crises but also, to be effective in the treatment of acute chest syndrome, and in reducing overall mortality in adult patients[19,20,21].

FOLIC ACID

Folate is a water-soluble B vitamin needed for erythropoiesis (the Process which produces red blood cells) Given there is increased erythropoiesis in people with sickle cell disease.

Folic acid is widely prescribed for SCD with the rationale that increased erythropoiesis caused an increased risk of folate deficiency. Children with sickle cell disease will undergo close observation by the pediatrician and will require management by a hematologist to assure they remain healthy. This patient will take a 5mg dose of folic acid daily for life[1].

It is necessary to use it daily. Because of folate deficiency.

CRIZANLIZUMAB (ADOKVEO)

Crizanlizumab is an immunoglobin G2 kappa Monoclonal antibody that binds to P-selection, Blocking its interaction with P-selection glycoprotein ligand 1.

Crizanlizumab is a treatment injected into the vein (intravenous or IV) that people with sickle cell can take on its own or alongside hydroxycarbamide (also known as hydroxyurea), to prevent episodes of pain and some other complication in people with sickle cell. Crizanlizumab is a monoclonal antibody that targets selection to reduce the frequency of vasooclusive crises in patients with sickle cell disease.

L-glutamine :

L-glutamine is a naturally occurring amino acid. It increases NAD redox potential in sickle red blood cells by increasing the availability of reduced glutathione.

Glutamine is a conditionally essential amino acid, meaning that although the body normally makes sufficient amounts, at times of stress the body's need for glutamine increases. The U.S. Food and Drug Administration (FDA) approved the use of pharmaceutical-grade L-glutamine for sickle patients aged five years or older in July 2017[2,22]. Formal clinical trials showed that this purified version of glutamine significantly reduced the frequency of acute complications of SCD[15,22].

Sickle cell disease patients treated with oral L-glutamine for at least four weeks had reduced adhesion of sickle erythrocytes to human umbilical vein endothelial cells compared to untreated patients.

Treatment of Sickle Cell Disorder by Ayurvedic Medicine

'Yogaraj and Laxadi guguly' are two ayurvedic medicine has been used for the maintenance of hemoglobin levels and prevention of repeated blood transfusion in sickle cell disorder.

The drugs Yogaraj has classical references and are used as hepato protecting action, blood purifiers, decreasing in hepatosplenomegaly and chronic fever which as a whole helps in pitta vicars. Lakshyadi gugulu is used as the best bone unioner which also reduces pain (vitiated vayu) inside the bone marrow and helps in erythropoiesis. Sickle cell disorders are due to the vitiation of vayu and pitta. So these two drugs help to stable the above doshas. Patients were treated with Lakshyadi gugulu after food with warm

water and Yogaraj with honey. The preparation of medicine was as prescribed in vaisajyaratna in a combination of indigenous medicines, folic acid (Folate) 5gm once daily is a supplement[23].

BONE MARROW TRANSPLANT

BMT is the only current cure for SCD and is one of the newer methods of treatment available. Results indicate an event-free survival rate of approximately 91% and a mortality rate of less than 5%[24]. BMT carries significant risks, such as the new bone marrow producing leucocytes attacking hosts tissues cells which are known as Graft-versus-host-disease (GVHD)[25]. The risk of 17 developing GVHD is low when the donor and the recipient are related and matched for HLA(Human Leukocyte Antigen) type.

GENE THERAPY

Gene therapy is in early studies as a possible cure for sickle cell anemia. The approach is based on steam cell and gene therapy; instead of using embryonic stem cells, host stem cells are derived by manipulating and reprogramming cells from the patient's own blood cell with genetic engineering used to correct the inborn genetic error. Because the cell is provided by the patient, there is no need to find another person to serve as a donor of stem cells and there should be no risk of GVHD. The aim is to transform a patient's blood cells into pluripotent stem cells and replace the defective portion of the gene[26].

Health maintenance for a patient with sickle cell disease starts with early diagnosis, preferably in the newborn, period and increased penicillin prophylaxis, vaccination against pneumococcus bacteria, and folic acid supplement. Treatment of complications often includes antibiotics, pain management, intravenous fluids blood transfusion.

BLOOD TRANSFUSION

These are used to treat and prevent complications, such as stroke, in people with sickle cell disease.

In a red blood cell transfusion, red blood cells are removed from a supply of donated blood, then given through a vein to a person with sickle cell anemia. This increase the number of normal red blood cells, which helps reduce symptoms and complications.

Ricks include an immune response to the donor blood, which can make it hard to find future donors; infection; and excess iron build-up in your body. Because excess iron can damage your heart, liver, and other organs, you might need treatment to reduce iron levels if you undergo regular transfusions.

CONCLUSION

Sickle Cell Anemia is a homozygous form of HbS (HbSS). This result from single point replacement of glutamic by valine at position 6 to β globin chain. This reduces the solubility of the red cells which in turn leads to polymerization and vaso occlusion in the vasculature. The association of two mutant β globin subunits forms hemoglobin S (HbS). Under low oxygen condition, the absence of a polar amino acid at the position of six of the β globin chain promotes the non-covalent polymerization of hemoglobin, which distorts red blood cells into a sickle shape and decrease their elasticity. Sickle cell disease is a chronic, debilitating disorder with a myriad of symptoms that make disease treatment challenging. While there is a need for new treatments for sickle cell disease, especially for disease modifying agents, there is also a need to explore new approaches for improving treatment with existing modalities.

REFERENCE

[1] Obeagu, Emmanuel Ifeanyi, Ochei, K. C., Nwachukwa, B. N., Nehuma, Blessing Ogechi "Sickle Cell Anamia: A Review" Emmanuel OF et al., Sch. J. App. Med. Sci., September 2015; 3 (6B): 2244-2252

[2] Baba P. D. Inusa , Lewis L. Hsu , Neeraj Kholi , Anissa Patel, Kilali Ominu- Evbota , Kofi A. Anie and wale Atoyebi " Sickle Cell Disease – Genetic, Pathophysiology, Clinical Presentation and Treatment" Neonatal Screening 2019, 5, 20; doi 103390

[3] J. Makani, S. F. Ofoi- Acquahb, O. Nnodu , A. Wonkam, and K. Othene-Frempong " Sickle Cell Disease: New opportunities and Challenges in Africa" Hindawi Publishing Corporation The scientific World Journal Volume 2013

[4] Hoflman R, Benz JE, Shantil SJ, Furine B. Cohen HJ, Silberaterin LE: Methemoglobinemia in Haematology Basic Principle and Practice. 2nd Ed. U.S.A : Churchilli livingstone Inc, 1995.

[5] Deepika S. Darbari, Vivien A. Sheehan, Samir K. Ballas "The Vaso-Occlusive pain crisis in sickle cell disease: Definition, pathophysiology and

management"., wileyonlinelibrary.com journal., Eur J Haematol. 2020

[6] Ballas SK, Lusardi M. Hospital readmission for adult acute sickle cell painful episodes: frequency, etiology, and prognostic significance. Am J Hematol. 2005;79:17-25.

[7] Platt OS. Brambilla DJ, Rosse WF et al Mortality in sickle cell disease: life expectancy and risk factors for early death N Engl J Med 1994;330;1639- 1644

[8] O. S. Platt, B. D. Thoringtone , D. J. Brambilla et al ., "Pain In Sickle cell disease -rate and risk factor" The new England journal of Medicine, Vol. 325, no 1 ,pp.11-16,1991

[9] Bainbridge R, Higgs DR, Maude GH, Serjeant, GR; Clinical Prsentation of Homozygous Sickle Cell Disease. J. Paediatr, 1985; 1067: 881

[10] Brozovic M, Davlas S, Brownell; Acute Admissions of Patients with Sickle Cell Disease Who Live in Britain. Br. Med. J., 1987; 294: 1206.

[11] Cameron K. Tebbi., "Sickle cell Disease, A Review"., Hemato 2022, 3(2), 341-366; https: //doi.org/10.3389/hemto3020024

[12] Howard, J.; Hart, N.; Roberts-Harewood, M.; Cummins, M.; Awogbade, M.; Davis B. The BCSH Committee Guideline on the management of the acute chest syndrome in sickle cell disease. Br. J. Hematol. 2015, 169, 492- 505[Pubmed]

[13] Charache, S.; "Acute chest syndrome" in adult with sickle cell anemia. Microbiology, treatment, and prevention. Arch. Intern. Med 1979,139,76-68.

[14] Britton JC; Disorder of the blood: Diagnosis, pathology, Treatment and Technology. J. and A. Chruchill Ltd, 1909; 102-110.

[15] Gardene, R.V. Sickle cell Disease; Advance in treatment. Ochsner J 2018,18,377-389 doi: 10. 31486/toj.18.0076. [PMC free article] [PubMed]

[16] Tim Jang, Mana Poplawaska, Emmanuela Cimpeanu, George Mo, Dibyendu Dutta and Seah H. Lim,; "Vaso-Occlusive crisis in sickle cell disease: a vicious cycle of secondary events.; Jang et al J transl Med (2021) 19-397

[17] BeiterJL Jr, Simon HK, Chambliss CR, Adamkiewicz T, Sullivan K. Intravenous ketorolac in the emergency department management of sickle cell pain and predictors of its effectiveness. Arch Pediatr Adolesc Med. 2001; 155:496-500

[18] Centers for Disease Control and Prevention (CDC). Sickle cell data collection data brief: Hydroxyurea use among Medicaid benefciaries with sickle cell disease in California and Georgia, 2006–2016. November 13, 2019; https://www.cdc.gov/ncbddd/hemoglobinopathies/scdc-hydroxyurea-data-brief.html.

[19] Kathleen A. Neville , M.D., M.S. , and Julie A. Panepinto, M.D., M.S.P.H " Pharmacotherapy of sickle cell disease" , 18th Expert Committee on the selection and use of essential medicine .

[20] Charche S, Terrin ML, Moore RD, et al Effect of Hydroxyurea on the Frequency of Painful crises in sickle cell anaemia. Investigator of the Multicentre Study of Hydroxyurea in Sickle cell Anaemia. N Engle J Med 1995;332: 1317-22.

[21] Steinberg M, Bartoon FB, Castro O, et al . Effect of hydroxyurea on mortality and morbidity in adult sickle cell anaemia. Risk and benefits up to 9 years of treatment. JAMA 2003;289: 1645-51.

[22] Niihara Y., Miller S.T., Kanter J., Lanzkron S., Smith W.R., Hsu L.L., Gordeuk V.R., Viswanathan K., Sarnaik S., Osunkwo I., Guillaume E. A phase 3 trial of L-glutamine in sickle cell disease. *N. Engl. J. Med.* 2018; 379:226–235. doi: 10.1056/ NEJMoa171 5971. [PubMed]

[23] Hemant Kumar Panigrahi, Hemant Kushawa and Shyam Sunder Sharma., "Treatment of Sickle cell Disorders by Ayurvedic Medicine" Ancient Science of life., Vol. No 17(1),July 1997. [PubMed]

[24] National Heart Lung and Blood Institute Evidence-Based Management of Sickle Cell Disease: Expert Panel Report. [(accessed on 10 February 2019)];2014 Available online: https: //www.nhlbi.nih.gov/health-topics/evidence-based-management-sickle-cell-disease

[25] Kassim A.A., Sharma D. Hematopoietic stem cell transplantation for sickle cell disease: The changing landscape. Ther. 2017;10:259–266. doi: 10.1016/j.hemonc.2017.05.008.

[26] Ribeil J.A., Hacein-Bey-Abina S., Payen E., Magnani A., Semeraro M., Magrin E., Caccavelli L., Neven B., Bourget P., El Nemer W., et al. Gene therapy in a patient with sickle celldisease. *N. Engl. J. Med.* 2017;376:848–855. doi: 10.1056/NEJMoa1609677.