IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 25, Issue 7 Ser. 1 (July. 2026), PP 105-110
www.iosrjournals.org

A Systematic Review on Sickle Cell Anemia

S. Asifa[1], Afroja Sabnam[2], Nahidha Khanam[3], S. Naziya[4]
[1.] *B. Pharmacy. Krishna Teja Pharmacy College*
[2.] *Masters in Biotechnology, North Orissa University*
[3.] *Doctor of Pharmacy (Pharm.D), Krishna Teja Pharmacy College*
[4.] *DNB General Medicine. Assistant Professor. SRM Medical College Hospital and research centre*

Abstract:
Sickle cell anemia is a genetic disorder affecting the globin chains, causing hemolysis and long-term organ damage. It is the most common form of sickle cell disease (SCD), marked by lifelong hemolytic anemia, frequent blood transfusions, pain crises, and organ complications. [1]This overview discusses the disease's pathophysiology, symptoms, complications, diagnosis, and treatment, highlighting the vital role of the healthcare team in patient care.[2]
SCD is a genetic blood disorder where abnormal hemoglobin causes red blood cells to become sickle- or crescent-shaped. It affects millions worldwide, mostly those of African, Mediterranean, Middle Eastern, and South Asian descent. The disease arises from a gene mutation that produces hemoglobin S, making red blood cells rigid and sticky, leading to pain, fatigue, anemia, and increased infection risk.[3] Treatment focuses on symptom control and preventing complications through pain relief, hydration, and blood transfusions to improve oxygen delivery. Hydroxyurea, a medication that increases fetal hemoglobin, is commonly used to reduce pain episodes. [4]In severe cases, bone marrow or stem cell transplants may offer a cure. Understanding these aspects is crucial for healthcare providers, patients, and families to promote early diagnosis, effective treatment, and better quality of life.[5]
Sickle cell anemia specifically results from a single mutation where valine replaces glutamine at position 6 of the β-globin chain, reducing red blood cell solubility and causing polymerization and vessel blockage.[6] The β-globin gene is on chromosome 11's short arm. Hemoglobin S forms when two mutant β-globin subunits combine. Under low oxygen, lack of a polar amino acid at position six causes hemoglobin to polymerize, deforming red blood cells into sickle shapes and reducing their elasticity.[7] These rigid cells cannot pass easily through capillaries, causing ischemia and vessel occlusion. The anemia stems from hemolysis, the destruction of these misshapen cells in the spleen.[8] Chronic anemia affects those with the condition, while individuals with normal hemoglobin would not survive due to spleen-mediated destruction of the abnormal cells.[9]

I. Introduction:

Although sickle cell disease (SCD) was recognized under various names in Africa, the first case documented in Western medicine was reported by Herrick in 1910, involving Walter Clement, a dental student from Grenada. By 1949, Pauling identified sickle cell anemia as the first molecular human disease, and in 1956, Ingram discovered the specific amino acid substitution in the β-globin chain of hemoglobin S (HbS) [10-13].SCD consists of inherited autosomal recessive disorders caused by mutations in both copies of the β-globin gene (HBB) alongside the presence of HbS. The disease occurs in two genetic forms: homozygous (sickle cell anemia) and double heterozygous (co-inheritance of HbS with another HBB mutation). The type of SCD depends on the inherited genes from both parents, and co-inheritance of different mutations can affect disease severity. The three common types are HbSS (sickle cell anemia), HbSC, and HbS β-thalassemia (HbS β0 or HbS β+ thalassemia)[14].The disease pathology involves four main mechanisms: HbS polymerization, vaso-occlusion, endothelial dysfunction, and sterile inflammation. Polymerization of HbS inside red blood cells (RBCs) makes them rigid, less flexible, and fragile. Sickled RBCs live less than 20 days, compared to normal RBCs' 120 days, leading to chronic hemolytic anemia that can be severe and life-threatening[15]. These abnormal cells cause vaso-occlusion, with vaso-occlusive crisis (VOC) being the hallmark symptom and the leading cause of hospital visits among SCD patients. SCD causes various acute and chronic complications such as pain crises, delayed growth and puberty, infections, pregnancy complications, priapism, fatigue, osteonecrosis, dactylitis, kidney disease, pulmonary hypertension, splenomegaly, stroke, silent brain infarcts, acute chest syndrome, and multi-organ failure.[16]

Sickle cell disease affects about 100,000 people in the United States and over 3 million worldwide. It is characterized by chronic hemolytic anemia, severe acute and chronic pain, and progressive organ damage throughout life.[17]. The disease is linked to premature mortality, with a median age of death of 43 years (IQR 31.5–55 years)[18]Effective management requires early diagnosis, prevention of complications, and treatment of

organ damage. This review discusses recent advances in diagnosing and managing four major SCD complications: acute and chronic pain, cardiopulmonary disease, central nervous system disease, and kidney disease. It also highlights new developments in disease-modifying and potentially curative treatments.[19].

Pathophysiology:

Sickle Cell Anemia (SCA) mainly involves two key processes: Hemolysis and Vaso-Occlusive Crisis (VOC). A mutation in the beta-globin gene causes sickle cell hemoglobin (HbS) to form rigid, elongated polymers when deoxygenated. Initially, sickle cells alternate between a normal biconcave shape and an abnormal sickle shape under low oxygen, but eventually these changes become permanent, increasing risks of hemolysis and VOC. All sickle cell disease (SCD) types share this HbS polymerization process.

Deoxygenated sickle cells cause vascular occlusion, leading to local oxygen deprivation, tissue damage, and inflammation. Though caused by a single gene mutation, SCD triggers complex physiological effects resulting in symptoms such as inflammation, coagulation, oxidative stress, impaired arginine metabolism, anemia, and hemolysis. SCD is also an angiopathy associated with nutrient deficiencies that worsen patient health.[20]

The insoluble sickled hemoglobin polymerizes into tubulin fibers, making red cells rigid and prone to getting trapped in small blood vessels. This blockage deprives tissues of blood and oxygen, causing ischemic injury or cell death. Abnormalities in ion channels cause these cells to lose water and become dehydrated. They also show disrupted intracellular signaling, low nitric oxide and ATP levels, and reduced antioxidant capacity, leading to oxidative damage.

Oxidative stress damages cell membrane proteins, causing phosphatidylserine exposure and microparticle formation, which promote blood clotting.[21,22] During hemolysis, free hemoglobin released into plasma scavenges nitric oxide, and sickle cells have lower arginase 1 activity, limiting nitric oxide production, especially in individuals with high hemolysis rates. Hemolysis also generates reactive oxygen species, furthering cell damage.

Additionally, sickle cells experience microRNA dysregulation affecting gene expression during red blood cell formation[23]. Their abnormal stickiness activates adhesive receptors, and sickle hemoglobin-containing cells remain less flexible even when regaining a normal shape. Morphologically normal sickle cells also tend to adhere like permanently sickled cells.

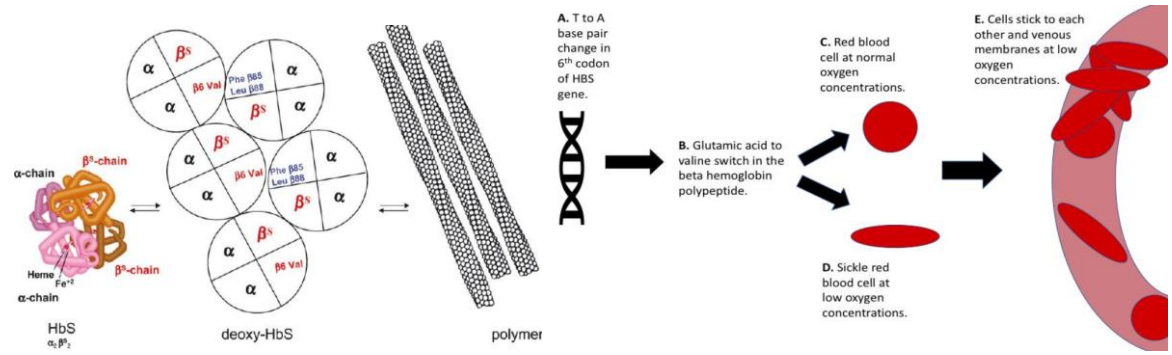

Fig:1**.** Pathophysiology of sickle cell disease showing hemoglobin S polymerization, red blood cell sickling.

Simplified Flow Diagram: HbS→ Polymerization→ Sickling →Vaso-Occlusion+ Hemolysis→ Ischemia+ Inflammation→ Organ Damage

Sickle Cell Disease Symptoms

Symptoms typically begin after six months of age and vary depending on the severity of the hemoglobin gene mutation, which differs by ethnicity or geographic region. For example, sickle cell variants in Africa tend to be more severe than those in some Indian populations. Common triggers include dehydration, low oxygen levels, oxidative stress, and acute illness causing blood acidosis. These triggers cause sickle hemoglobin to polymerize, changing red blood cells (RBCs) into a sickle (half-moon) shape, a process called "sickling." Symptoms depend on the amount of sickle hemoglobin present.

Major acute symptoms include:

- **Anemia:** Caused by destruction of misshapen sickle RBCs, leading to low hemoglobin and jaundice. Chronic RBC destruction can cause gallstones due to hemoglobin waste buildup.
- **Vaso-occlusive (Pain) Crisis:** Repeated pain episodes result from blockage of small blood vessels by inflexible sickle cells, leading to pain and tissue ischemia. Commonly affects hands and feet (dactylitis), causing swelling and pain.

- **Infections:** Frequent fevers arise from infections often affecting the lungs, bones, and bloodstream. The spleen, rich in small blood vessels, becomes damaged as sickle cells block vessels, weakening immune defenses and increasing infection risk.
- **Stroke:** Blockage of brain vessels can cause strokes with symptoms like seizures, limb weakness or numbness, speech difficulties, and unconsciousness.
- **Acute Chest Syndrome (ACS):** The leading cause of death in SCD, presenting with cough, breathlessness, and sometimes fever (which may indicate pneumonia)

Chronic complications include:

- **Iron overload:** From repeated blood transfusions, iron builds up in organs such as the heart, lungs, and glands, impairing their function.
- **Avascular necrosis:** Blocked blood flow in bone capillaries, often in hips, causes bone death, pain, and disability.
- **Leg ulcers:** Typically on ankles, worsened by severe anemia, infections, and trauma.
- **Pulmonary artery hypertension:** Causes breathlessness on exertion and leg swelling.
- **Chronic kidney disease:** Occurs in about 30% of adults with SCD due to repeated blood vessel blockages in kidneys.
- **Sickle retinopathy:** Repeated retinal vessel blockages cause new fragile blood vessels to form and bleed, affecting vision.

Diagnosis

Suspected in children based on symptoms and family history, confirmed by blood tests such as complete blood count, peripheral smear (showing sickle cells), and high-performance liquid chromatography (HPLC) for sickle hemoglobin detection. Newborn screening identifies SCA early in high-income countries.

Treatment

- **Hematopoietic Stem Cell Transplant (HSCT/BMT):** The only cure by replacing defective stem cells. Gene therapy is experimental and not widely available, so BMT is the main curative option in India, with cure rates of 80-90%[24].
- **Supportive care:** Includes oxygen for low oxygen levels, hydration to prevent sickling, pain management with NSAIDs and opioids, prompt antibiotic treatment for fever due to immune deficiency, and blood transfusions to reduce sickle hemoglobin during anemia or complications.
- **Hydroxyurea:** An oral medication that increases fetal hemoglobin to reduce sickle hemoglobin, lowering complication frequency. Recommended for infants older than 9 months, children, and adolescents, with regular blood monitoring.
- **Newer drugs:** Voxelotor (oral) and Crizanlizumab (injectable) show promise but are costly and less available in India.[25,26]
- **Preventive care:** Includes prophylactic antibiotics (e.g., penicillin) and vaccinations against infections like pneumococcus, meningococcus, and H. influenza.

Patients experiencing pain, fever, cough, breathing problems, sudden weakness, or numbness should seek immediate medical attention. Adequate hydration, vaccinations, and preventive antibiotics are essential to avoid complications. For frequent or severe symptoms, BMT offers a long-term cure.

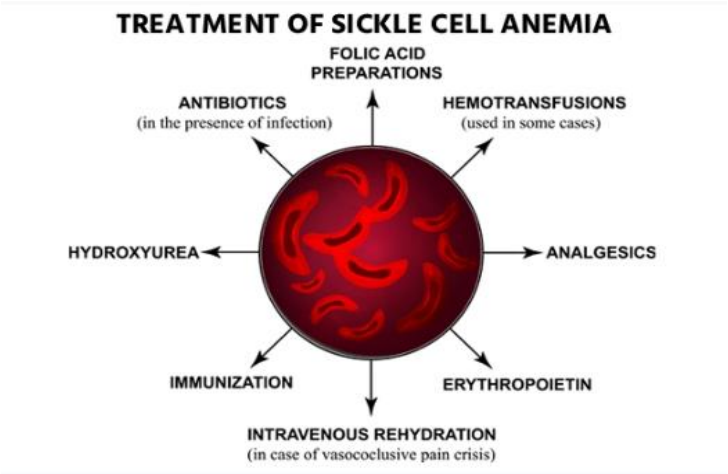

Fig 2: Treatment and Management of Sickle Cell Anemia.

Complication-specific treatments
Antibiotics:
Prophylactic antibiotics like penicillin are commonly given to children with SCD to prevent infections, particularly those caused by *Streptococcus pneumoniae*. Vaccinations against common bacterial infections such as pneumococcus and meningococcus are also advised.

Transfusion therapy:
Regular blood transfusions may be recommended for patients experiencing complications like stroke or recurrent ACA. Transfusions help reduce these risks by lowering the proportion of sickled cells and improving the blood's oxygen-carrying capacity.[27]

Pulmonary hypertension management:
For SCD patients with pulmonary hypertension, targeted treatments including endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs may be used to ease symptoms and slow disease progression.[28]

Psychosocial Issues
Recent understanding of the psychosocial adjustment in patients with sickle cell disease has reached a level that allows for targeted intervention [29]. Although most patients adapt well, the disease is linked to increased risks of depression, low self-esteem, social isolation, strained family relationships, and withdrawal from everyday activities [30, 31]. Those who adjust well typically use active coping strategies and receive strong support from their family and extended family networks, which are common in African-American communities [32]. Intervention efforts should focus on recognizing and building individual strengths, addressing problematic behaviors, and developing coping skills by reframing pain, shifting attention away from pain, and leveraging support systems.

Mangement of Sickle Cell Anemia:
Medical Management
Medications: Treatment for sickle cell disease often focuses on managing pain and anemia symptoms, which may involve rest, intravenous fluids, and pain relief medications. Hydroxyurea is a commonly prescribed drug that boosts hemoglobin production and reduces the frequency of acute episodes. It also increases the water content in red blood cells and improves the flexibility of sickled cells, helping them pass more easily through small blood vessels. Clinical trials have shown that hydroxyurea lowers the number of painful crises, hospital stays, occurrences of acute chest syndrome, and the need for blood transfusions.
Medical interventions are also necessary to handle various systemic complications of the disease. For instance, blood transfusions treat conditions like acute stroke or acute chest syndrome related to sickle cell disease[33]. Treatments such as hydroxyurea, vasodilators, and anticoagulants are used for pulmonary hypertension in these patients.
Research has explored using fetal hemoglobin to treat sickle cell disease. Introducing normal hemoglobin helps prevent red blood cells from sickling and reduces painful episodes later in life.[34]
Genetic Counseling: Couples who may carry the sickle cell trait can access genetic counseling. Counselors provide information about the chances of having a child with sickle cell disease or trait and discuss different options available.[35]
Bone Marrow Transplant: Bone marrow transplantation is a successful cure for sickle cell disease, allowing the body to produce normal red blood cells. Improvements in neurological and lung function have been observed after the transplant. Since its first use in 1984, studies show that 78% of patients remained disease-free four years post-transplant. However, this treatment is not accessible to all due to risks like donor rejection or graft-versus-host disease. New methods, such as using a "facilitating cell" during transplant (developed by Dr. Suzanne Ildstad at the University of Louisville), are being researched to reduce these risks and improve transplant success.

Avoiding adverse climatic conditions: The most common trigger for painful crises is exposure to cold. Educating patients about the importance of staying warm, especially during cold, wet seasons and at night, along with wearing appropriate clothing, can help reduce the risk.
Hydration: Dehydration and increased blood concentration can lead to painful crises in some patients. Maintaining proper hydration is crucial, particularly during fever or in hot climates where fluid loss is higher.
Oxygen: Oxygen therapy is often recommended during acute complications. Patients with sickle cell disease typically have lower arterial oxygen levels, which can worsen during illnesses like acute chest syndrome. Providing high levels of oxygen in these cases is beneficial.[36]
Education: Two key areas of education are essential for children with sickle cell disease: understanding their condition and continuing formal education. Being informed about the disease helps patients manage it better and

handle mild painful episodes at home with reassurance and support. Teaching the importance of wearing shoes and socks may also help reduce the risk of trauma-related leg ulcers.[37]

II. Conclusion:

Sickle cell anemia is a serious inherited hemoglobin disorder caused by a mutation in the β-globin gene, resulting in the formation of abnormal hemoglobin S and sickling of red blood cells. The disease is characterized by chronic hemolytic anemia, recurrent vaso-occlusive crises, inflammation, and progressive multi-organ damage, leading to significant morbidity and reduced life expectancy. Clinical manifestations range from painful crises, infections, acute chest syndrome, and stroke to long-term complications affecting the kidneys, lungs, bones, eyes, and cardiovascular system.

Advances in understanding the molecular and pathophysiological mechanisms of sickle cell disease have improved diagnostic approaches and treatment strategies. Early diagnosis through newborn screening and laboratory investigations, combined with comprehensive management involving hydroxyurea therapy, blood transfusions, infection prevention, pain control, and supportive care, has significantly enhanced patient outcomes. Hematopoietic stem cell transplantation remains the only established curative treatment, while emerging therapies such as gene therapy and novel disease-modifying agents offer promising future prospects.

In addition to medical management, psychosocial support, genetic counseling, patient education, adequate hydration, and preventive healthcare measures play crucial roles in improving quality of life and reducing disease-related complications. A multidisciplinary approach involving healthcare professionals, patients, families, and community support systems is essential for effective disease management. Continued research and improved access to advanced therapies are vital to reducing the global burden of sickle cell anemia and achieving better long-term outcomes for affected individuals

References:

[1]. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet*. 2010;376(9757):2018- 2031. doi:10.1016/S0140-6736(10)61029-X.

[2]. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med*. 2017;376(16):1561-1573. doi:10.1056/NEJMra1510865.

[3]. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. *Nat Rev Dis Primers*. 2018;4:18010. doi:10.1038/nrdp.2018.10.

[4]. Bunn HF. Pathogenesis and treatment of sickle cell disease. *N Engl J Med*. 1997;337(11):762-769. doi:10.1056/NEJM199709113371107.

[5]. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. 1994;330(23):1639-1644. doi:10.1056/NEJM199406093302303.

[6]. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. *Lancet*. 2017;390(10091):311-323. doi:10.1016/S0140-6736(17)30193-9.

[7]. Mangla A, Agarwal N, Maruvada S. Sickle Cell Anemia. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.

[8]. Elendu C, Amaechi DC, Alakwe-Ojimba CE, Elendu TC, Elendu RC, Ayabazu CP, et al. Understanding sickle cell disease: Causes, symptoms, and treatment options. *Medicine (Baltimore)*. 2023;102(38):e35237. doi:10.1097/MD.0000000000035237.

[9]. Steinberg MH. Management of sickle cell disease. *N Engl J Med*. 1999;340(13):1021-1030. doi:10.1056/NEJM199904013401307.

[10]. Ingram VM. Gene mutations in human haemoglobin: the chemical difference between normal and sickle cell haemoglobin. *Nature*. 1957;180(4581):326-328. doi:10.1038/180326a0.

[11]. Herrick JB. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. **Arch Intern Med**. 1910;6(5):517-521.

[12]. Savitt TL, Goldberg MF. Herrick's 1910 case report of sickle cell anemia: the rest of the story. **JAMA**. 1989;261(2):266-271.

[13]. Pauling L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia, a molecular disease. **Science**. 1949;110(2865):543-548.

[14]. Stuart MJ, Nagel RL. Sickle-cell disease. **Lancet**. 2004;364(9442):1343-1360.

[15]. Hassell KL. Population estimates of sickle cell disease in the U.S. **Am J Prev Med**. 2010;38(4 Suppl):S512-S521.

[16]. Lanzkron S, Carroll CP, Haywood C Jr. Mortality rates and age at death from sickle cell disease: U.S., 1979–2005. **Public Health Rep**. 2013;128(2):110-116.

[17]. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. **JAMA**. 2014;312(10):1033-1048.

[18]. Kanter J, Kruse-Jarres R. Management of sickle cell disease from childhood through adulthood. **Blood Rev**. 2013;27(6):279-287.

[19]. Niihara Y, Miller ST, Kanter J, Lanzkron S, Smith WR, Hsu LL, et al. A phase 3 trial of L-glutamine in sickle cell disease. **N Engl J Med**. 2018;379(3):226-235.

[20]. Sundd P, Gladwin MT, Novelli EM. Pathophysiology of sickle cell disease. **Annu Rev Pathol**. 2019;14:263-292.

[21]. Manwani D, Frenette PS. Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies. *Blood*. 2013;122(24):3892–3898.

[22]. Gladwin MT, Kato GJ. Intravascular hemolysis and the pathophysiology of sickle cell disease. *J Clin Invest*. 2017;127(3):750–760.

[23]. Conran N, De Paula EV. Thromboinflammatory mechanisms in sickle cell disease. *Haematologica*. 2020;105(10):2393–2404.

[24]. Connes P, Alexy T, Detterich J, Romana M, Hardy-Dessources MD, Ballas SK. The role of blood rheology in sickle cell disease. *Blood Rev*. 2016.

[25]. Walters MC, Patience M, Leisenring W, Rogers ZR, Aquino VM, Buchanan GR, Roberts IA, Yeager AM, Vichinsky E, Sullivan KM. Bone marrow transplantation for sickle cell disease. *N Engl J Med*. 1996;335(6):369–376. doi:10.1056/NEJM199608083350601.

[26]. Vichinsky EP, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A, Hassab H, Achebe MM, Alkindi S, Brown RC, Inati A, Kutlar A, Kanter J, Minniti CP, Lehrer-Graiwer J. A phase 3 randomized trial of Voxelotor in sickle cell disease. *N Engl J Med*. 2019;381(6):509–519. doi:10.1056/NEJMoa1903212.

[27]. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J, Guthrie TH, Knight-Madden J, Alvarez OA, Gordeuk VR, Gualandro S, Colella MP, Smith WR, Rollins SA, Stocker JW. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med*. 2017;376(5):429–439. doi:10.1056/NEJMoa1611770
[28]. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. *Blood Adv*. 2020;4(2):327-355.
[29]. Klings ES, Machado RF, Barst RJ, Morris CR, Mubarak KK, Gordeuk VR, et al. Diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. *Am J Respir Crit Care Med*. 2014;189(6):727-740.
[30]. Barbarin OA, Christian M. The social and cultural context of coping with sickle cell disease: I. A review of biomedical and psychosocial issues. *J Black Psychol*. 1999;25(3):277-293.
[31]. Ohaeri JU, Shokunbi WA, Akinlade KS, Dare LO. The psychosocial problems of sickle cell disease sufferers and their methods of coping. *Soc Sci Med*. 1995;40(7):955-960
[32]. Edwards CL, de C Williams AC, Loughlin C, et al. Psychosocial and affective comorbidities in sickle cell disease. *Neurosci Lett*. 2019;705:1-6.
[33]. Essien EA, Winter-Eteng BF, Onukogu CU, Nkangha DD, Daniel FM. Psychosocial challenges of persons with sickle cell anemia: a narrative review. *Medicine (Baltimore)*. 2023;102(47):e36147
[34]. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med*. 1995;332(20):1317-22. doi:10.1056/NEJM199505183322001.
[35]. Gluckman E, Cappelli B, Bernaudin F, Labopin M, Volt F, Carreras J, et al. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. *Blood*. 2017;129(11):1548-56. doi:10.1182/blood-2016-10-745711.
[36]. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. *Bull World Health Organ*. 2008;86(6):480-7. doi:10.2471/BLT.06.036673.
[37]. Serjeant GR. *Sickle Cell Disease*. 3rd ed. Oxford: Oxford University Press; 2001.
[38]. Centers for Disease Control and Prevention. Prevention and treatment of sickle cell disease complications. Atlanta (GA): CDC; 2024. Available from: CDC Sickle Cell Disease Prevention and Treatment.