Sickle cell disease and life-threatening infections

Mini Review

Dr. Salma M AlDallal
Email: dr.s.aldallal@outlook.com
Mobile: +965-90901477

***Abstract*— The prevalence of sickle cell disease (SCD) is a growing global health issue. It refers to an autosomal recessive illness characterized by intrinsically defective hemoglobin (HbS), which causes chronic hemolytic anemia and a number of serious clinical symptoms. Newborn screening, routine clinical follow-up, and measures taken to preclude sepsis and organ failure have expanded life span among those with SCD. Due to increasing pathogen exposures, an upsurge in co-morbidities such as malnutrition, lower immunization rates, and less access to comprehensive care, such as antibiotics administration and blood transfusion, infection continues to be the leading cause of overall mortality among SCD patients in resource constrained economies. Tackling these issues for SCD patients in poor conditions can therefore result in the biggest reductions in infection-associated mortality rate. The current article emphasizes on the infections connected to SCD as well as the specific treatments that can be used to treat the said condition.**

Keywords*— *sickle cell disease; prophylaxis, antibiotics; bacterial infections; viral infections; parasitic infections

I. INTRODUCTION

Sickle cell disease (SCD) is a single gene defect that results in a systemic illness that is severely distressing and marked by chronic anemia, acute painful events, organ infarction, persistent organ damage, and a markedly shortened life expectancy [1,2]. Valine is substituted for glutamine at the 6th amino acid position of the β-chain, resulting in the SCD phenotype. Sickle hemoglobin is the term referred to hemoglobin that bears this replacement for an amino acid. Patients with the sickle-chain mutation who also have additional specific sickle-chain mutations, such as sickle-thalassemia or hemoglobin C disease also tend to have the SCD phenotype [3]. SCD is a complex multifactorial illness marked by abnormal endothelial interconnections, systemic inflammation, oxidative stress, and stimulation of the coagulation system as well presence of disordered hemoglobin architecture. Infection-connected acute episodes such as splenic confinement, acute chest syndrome, stroke, aplastic and vasoocclusive emergencies, long-term impairment, and mortality might occur as a result of these abnormalities [4].

One of the most frequent reasons that might cause a dilemma in SCD is the associated infection. A variety of SCD problems might arise as a result of infection. Alteration taking place at the cellular level during infections make problems more likely. Leukocyte levels in circulation and those of inflammatory cytokines rise. Leukocytes and the vascular endothelium both express more adhesion molecules. Due to the fact that post-capillary venules experience microvascular blockage, leukocyte adherence may be the initial event in vaso-occlusive episodes [5]. Oxidative damage results from the production of cytotoxic proteins, which also release reactive oxygen radicals. When HbS is reoxygenated, the sickling mechanism can be reversed; however, if HbS concentration rises due to dehydration, severe polymerization and irreparable membrane damage ensue. The likelihood of sickling is also increased by infections' non-specific adverse effects, such as fever, anorexia, nausea, diarrhea and vomiting.

Most SCD patients reside in low-income nations where infection frequency and transmission rates are high. Considering the underlying immunodeficiency affiliated with SCD and the related high incidence of infections in developing nations, recent research on the proposed pathways causing red cell sickling and vaso-occlusive downturn in SCD patients with infections has focused on the complicated issue related to contagious diseases [6]. In many nations, screening program for the newborn, routine clinical follow-up, and measures to preclude sepsis and organ damage have expanded life expectancy among those with SCD; nevertheless, in resource-constrained settings, where the vast bulk of affected children are born, most of them continue to lose their lives in infancy, typically without being diagnosed, as a result of the paucity of effective programs for its early recognition and treatment. It is crucial to correctly acknowledge the substantial burden of SCD in resource-poor nations when medical breakthroughs become available with the ability to treat or perhaps cure the said illness.

The present piece of article focuses on the infections associated with SCD along with the specific therapies that are available to curtail the said disorder.

II. INFECTIONS ASSOCIATED WITH SCD

A. Bacterial infections

S. pneumoniae, H. influenzae, and N. meningitidis are the three main causative microbes for the

incidence of meningitis. Children with SCD are also susceptible to meningitis caused by Salmonella species, E. coli, and other Gram-negative enteric bacteria, which must be taken into account while making the diagnostic evaluation. Meningitis in children under the age of five who do not have SCD typically manifests and develops identically to meningitis in children with SCD [7]. However, meningitis in children with SCD may increase their risk of stroke, a common side effect of the said disease [8].

Bacteremia manifests in a spectrum of aggressiveness, from mild to fulminant. More than 60% of all isolates were noted to be gram-negative bacteria; the most common isolates were Klebsiella pneumonia, Staphylococcus aureus, and Salmonella species [9]. According to research collected from both high income countries and low- to middle-income nations, the prevalence of bacteremia ranges from 6 to 25% and develops to a life-threatening condition in approximately 10–25% of children [10]. These findings imply that, following vigorous therapy, a considerable number of patients with SCD continue to face a serious risk of death from bacteremia, which is not the most frequent cause of fever in this population. It seems sense to believe that inadequate immunization, antibiotic prophylaxis, quick hospital transfer, intravenous antibiotics administration, blood supply, microbiologic diagnostic methods, and intensive care capacity in harsh conditions contribute to a rise in mortality and morbidity from bacteremia incidences.

In children with SCD, the pneumococcus is most frequently responsible for bacteremia and meningitis. Because of the impairment of splenic filter functioning driven on by infarction, the occurrence of invasive pneumococcal illness is known to be much higher in SCD patients compared to the normal population. In children under the age of three, prophylactic oral penicillin significantly cut down the risk of invasive pneumococcal illness. Therefore, fatal pneumococcal sepsis in children with SCD in developed economies is now uncommon [11].

S. aureus and Salmonella species account for 42–57% of all infectious causes of acute osteomyelitis [12]. Osteomyelitis frequently impacts the femur, tibia, or humerus' diaphysis. But after hematogenous expansion, any bone can be impacted, and it might be widespread [13]. By doing a bone biopsy, blood testing, or aspiration of a bone lesion, the causative microorganism can be determined [14]. Children with SCD may develop septic arthritis, which has microbes that are identical to those that cause osteomyelitis and osteonecrosis [15].

B. Viral infections

In SCD patients, the prevalence of HIV seropositivity has been reported to range between 0% to 11.5% [16]. There is minimal information on the effects of HIV infection and SCD coexistence, yet both conditions raise the risk of stroke, splenic malfunction, avascular necrosis, and pulmonary arterial hypertension incidences (98). Patients with SCD who also have HIV may be more vulnerable to encapsulated bacterial infections and opportunistic pathogen infections. Due to the augmentation of inflammation, rate of iron metabolism as well as auto-splenectomy, which are not conducive for HIV replication, SCD may provide defense against occurence of HIV infection [3].

Hepatitis C virus (HCV) positivity is present in at least 10% of adult with SCD, and liver damage is highly prevalent in the stated cases [17]. Though transfusion-acquired infections have become less common, the possibility of such incidence still exists. The amount of transfusions administered has a direct correlation with the HCV antibody positivity [18]. The liver damage induced on by HCV infection is exacerbated by iron buildup after blood transfusions.

Globally, SCD patients experience severe morbidity from other viruses such Parvovirus B19, hepatitis B, hepatitis C, Epstein - Barr virus, influenza, dengue [10]. In approximately 65 to 80% of infections in SCD patients, parvovirus B19 induces a temporary aplastic crisis. Severe anemia is caused by a temporary stoppage of erythropoiesis because it preferentially attacks erythroid progenitor cells. Acute chest syndrome, splenic and hepatic confinement, bone marrow necrosis, pain distress, and stroke have all been linked to parvovirus B19 [19].

Infection with the Epstein-Barr virus can result in SCD symptoms notably hemophagocytic lymphohistiocytosis, thrombocytopenia, agranulocytosis, hemolytic anemia, and splenic rupture. Individuals with SCD are at an increased risk of developing problems from influenza infections; their rate of hospitalization for influenza is reported to be significantly higher than that of children without SCD [20]. Hepatitis B and C, as well as HIV infections, can have a negative impact on the liver [14]. The blood circulation is a key reservoir of these said infections in locations with a lack of resources, but risky injections administered by inexperienced or unofficial practitioners and surgical procedures like circumcision and female genital mutilation are also potential routes through which hepatitis C is spread [21].

C. Infections caused by parasites

A protozoan parasite from the Plasmodium family that causes malaria is spread through blood transfusions, infected needles, and mosquito bites from the Anopheles mosquito. Since sickled erythrocytes are easily removed by splenic macrophages, it is thought that the sickle cell trait protects against persistent, life-threatening malaria [14]. Nevertheless, malaria has a serious impact on the morbidity and mortality of homozygous SCD patients, with fatality in the SCD cohort being much higher than that of malaria in those without SCD [22]. Studies in two African countries showed that while the risk of death was considerably higher in malaria patients with SCD as contrasted to those without, the prevalence of malaria was not elevated among those with SCD.

Due to their weakened immune system's ability to fight off infection, SCD patients have been found to have a higher incidence of protozoan and helminthic intestinal parasites [23]. Red cell sickling and vaso-occlusive crisis are predisposed by enhanced cell

adherence to vascular endothelium in pneumonitis-induced hypoxia and elevated eosinophil numbers as a result of tropical parasite infections [24].

III. THERAPIES FOR SCD RELATED INFECTIONS

In high-income nations, screening systems have been launched, and in lower-income nations with a high prevalence of SCD, development has just begun. Table 1 summarizes the treatment plan (including preventative therapy) for infections linked to SCD.

IV. CONCLUSION

The prevalence of SCD worldwide justifies a major focus on infection control. Even though it is widely acknowledged that encapsulated bacterial agents are the most significant microorganisms linked to serious sickness, there is proof that SCD raises the risk for a number of other infections, necessitating supplemental preventive strategies. Through the creation of suitable public health policies, better risk factor recognition in this situation could immediately effect preventing complications in patient populations with SCD. The risk of illness can be decreased by taking easy steps like improving cleanliness with hand washing, avoiding food contamination, and taking nutritional supplements. In developed nations, primary treatments like vaccines and penicillin prophylaxis have significantly improved health. Current findings added to the discussion over the necessity for pneumococcal vaccines in this milieu by demonstrating a different set of problems in underdeveloped nations with a wide spectrum of pathogens involved in serious illnesses. To insure that children benefit from the accessibility of ideal nutrition, disease-modifying drugs, prophylatic treatment with antibiotics, and immunization engagement, research into the obstacles that hinder adherence with vaccination and antibiotic prophylaxis is required. To maintain successful prophylaxis and immunization, continual surveillance into the emergence of microbial strains resistant to antibiotics and immunization strains is vital.

ACKNOWLEDGMENT

Not applicable

REFERENCES

[1] S. Chakravorty and T.N. Williams, “Sickle cell disease: a neglected chronic disease of increasing global health importance,” Arch. Dis. Child, vol 100, pp. 48-53, January 2015.

[2] B. Senapati, B. Das, S. Pradhan, A. Swain, A. Jaiswal, and N.K. Mohakud, “A hospital-based prospective study of sickle cell disease in children of eastern india.,” Med. J. D.Y. Patil Vidyapeeth, vol 0, pp. 0, 2022.

[3] D. Ochocinski, M. Dalal, L.V. Black, S. Carr, J. lew, and K. Sullivan, “Life-threatening infectious complications in sickle cell disease: a concise narrative review. Front Pediatr, vol 8, pp. 38, February 2020.

[4] D.J. Weatherall, “The inherited diseases of hemoglobin are an emerging global health burden," Blood. vol. 115, pp. 4331–4336, June 2010.

[5] D. Manwani and P.S. Frenette, “Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies,” Blood, vol 122, pp. 3892–3898, December 2013.

[6] S.G. Ahmed, “The role of infection in the pathogenesis of vaso-occlusive crisis in patients with sickle cell disease,” Mediterr. J. Hematol. Infect. Dis, vol 3, pp. e2011028, July 2011.

[7] C. Booth, B. Inusa, and S.K. Obaro, “Infection in sickle cell disease: a review,” Int. J. Infect. Dis, vol. 14, pp. e2–e12, January 2010.

[8] L.C. Jordan, J.F. Casella, and M.R. DeBaun, “Prospects for primary stroke prevention in children with sickle cell anaemia,” Br. J. Haematol, vol. 157, pp. 14–25, April 2012.

[9] B. Brown, H. Dada-Adegbola, C. Trippe, and O. Olopade, “Prevalence and etiology of bacteremia in febrile children with sickle cell disease at a Nigeria tertiary hospital,” Mediterr. J. Hematol. Infect. Dis, vol. 9, pp. e2017039, June 2017.

[10] G. Cannas, S. Merazga, and E.Virot, “Sickle cell disease and infections in high- and low-income countries,” Mediterr. J. Hematol. Infect. Dis, vol 11, pp. e2019042, July 2019.

[11] C.T. Quinn, Z.R. Rogers, T.L. McCavit, and G.R. Buchanan, “Improved survival of children and adolescents with sickle cell disease,” Blood, vol. 115, pp. 3447–3452, April 2010.

[12] R. Vaishya, A.K. Agarwal, E.O. Edomwonyi, and V. Vijay, “Musculoskeletal manifestations of sickle cell disease: a review,” Cureus, vol. 7, pp. e358, October 2015.

[13] J.B. Chambers, D.A. Forsythe, S.L. Bertrand, H.J. Iwinski, and D.E. Steflik, “Retrospective review of osteoarticular infections in a pediatric sickle cell age group,” J. Pediatr. Orthop, vol. 20, pp. 682–685, September-October 2000.

[14] A. Sobota, V. Sabharwal, G. Fonebi, and M. Steinberg, “How we prevent and manage infection in sickle cell disease,” Br. J. Haematol, vol. 170, pp. 757–767, September 2015.

[15] K.L. Vanderhave, C.A. Perkins, B. Scannell, and B.K. Brighton, “Orthopaedic manifestations of sickle cell disease,” J. Am. Acad. Orthop. Surg, vol. 26, pp. 94–101, February 2018.

[16] E.D. Owusu, B.J. Visser, I.M. Nagel, P.F. Mens, and M.P. Grobusch, “The interaction between sickle cell disease and HIV infection: a systematic review,” Clin. Infect. Dis, vol. 60, pp. 612–626, February 2015.

[17] M.F. Hasan, F. Marsh, G. Posner, R. Bellevue, H. Dosik, R. Suatengco, et al., “Chronic hepatitis C in patients with sickle cell anemia,” Am. J. Gastroenterol, vol. 91, pp. 1204–1206, June 1996.

[18] M. Hassan, S. Hasan, O. Castro, S. Giday, A. Banks and D. Smoot, “HCV in sickle cell disease,” J. Natl. Med. Assoc, vol. 95, pp. 864–874, September 2003.

[19] K. Smith-Whitley, H. Zhao, R.L. Hodinka, J. Kwiatkowski, R. Cecil, T. Cecil, et al., “Epidemiology of human parvovirus B19 in children with sickle cell disease,” Blood, vol. 103, pp. 422–427, January 2004.

[20] D.G. Bundy, J.J. Strouse, J.F. Casella, and M.R. Miller, “Burden of influenza-related hospitalizations among children with sickle cell disease,” Pediatrics. vol. 125, pp. 234–243, February 2010.

[21] S. El Katsha, S. Labeeb, S. Watts, and A. Younis, “Informal health providers and the transmission of hepatitis C virus: pilot study in two Egyptian villages,” East. Mediterr. Health J. vol. 12, pp. 758–767, November 2006.

[22] C.F. McAuley, C. Webb, J. Makani, A. Macharia, S. Uyoga, D.H. Opi et al., “High mortality from Plasmodium falciparum malaria in children living

with sickle cell anemia on the coast of Kenya. Blood, vol. 116, pp. 1663–1668, September 2010.

[23] N.K. Mahdi and N.H. Ali, "Intestinal parasites, including Cryptosporidium species, in Iraqi patients with sickle cell anaemia," East. Mediterr. Health J, vol. 8, pp.345–349, March-May 2002.

[24] S.G. Ahmed and U.A. Ibrahim, "A compendium of pathophysiologic basis of etiologic risk factors for painful vaso-occlusive crisis in sickle cell disease," Niger. J. Basic Clin. Sci, vol. 14, pp. 57–77, October 2017.

[25] J.D. Santoro, L. Myers, and J. Kanter, "Assessing the immunogenic response of a single center's pneumococcal vaccination protocol in sickle cell disease," J. Pediatr. Hematol. Oncol, vol. 38, pp. e102–e106, April 2016.

[26] L.H. Richards, J. Howard, and J.L. Klein, "Community-acquired Salmonella bacteraemia in patients with sickle-cell disease 1969–2008: a single centre study," Scand. J. Infect. Dis, vol. 43, pp. 89–94, February 2011.

[27] P. Hernigou, G. Daltro, C.H. Flouzat-Lachaniette, X. Roussignol, and A. Poignard, "Septic arthritis in adults with sickle cell disease often is associated with osteomyelitis or osteonecrosis," Clin. Orthop. Relat. Res, vol. 468, pp. 1676–1681, June 2010.

[28] A.P. Kourtis, P. Bansil, S.F. Posner, C. Johnson, D.J. Jamieson, "Trends in hospitalizations of HIV-infected children and adolescents in the United States: analysis of data from the 1994–2003 Nationwide Inpatient Sample," Pediatrics, vol. 120, pp. e236–e243, August 2007.

Table 1: Treatment plan (including preventative therapy) for infections linked to SCD

Infection	Antibiotics	Prophylactic regimen	References
Meningitis/CNS infection	• Third generation cephalosporins • Cryptococcus neoformans: Amphotericin B deoxycholate/ liposomal amphotericin B + fluocytosine, followed by fluconazole • Pasteurella multocida: penicillin • Capnocyphaga sp.: beta-lactam/beta-lactamase inhibitors and carbapenems	• Meningococcal B vaccination • Penicillin V prophylaxis • Erythromycin when penicillin related allergy shows up • Diphtheria/tetanus/pertussis/H. influenzae type B/polio/13-valent pneumococcal vaccine	[25,26]
Bacteremia/sepsis	• S. aureus infections: Oxacillin, nafcillin, or cefazolin • S. pneumoniae infections: Third generation cephalosporins	• Penicillin V prophylaxis • Erythromycin when penicillin related allergy shows up • Diphtheria/tetanus/pertussis/H. influenzae type B/polio/13-valent pneumococcal vaccine	[9]
Gastrointestinal infection	• Piperacillin-tazobactam/ carbapenem • Surgical consultation for open or laparoscopic cholecystectomy	• Vaccine against Salmonella Typhi when visiting endemic locations • Intake of hydroxyurea, ursodiol as well as low fat diet for lowering hemolysis/gallstone formation	[27]
Malaria	• Until the parasite density is less than 1% and the patient can tolerate oral medication, intravenous administration	• Patients in nations where malaria is endemic should get lifelong antimalarial chemoprophylaxis. • Refraining against being bitten by mosquitoes and staying away from places where mosquito-borne diseases are prevalent.	[3]

	of quinidine is recommended		
Human immunodeficiency infection	Consultation with an HIV specialist is advised as HIV related therapeutic options and recommendations alter over time and depend on the incidence of antiretroviral medication resistance and the profile associated side events.	• Following safe sex practices	[28]
Parasitic infections	• For helminth infections such as with *lumbricoides, A. duodenale*: intake of albendazole, mebendazole, and pyrantel pamoateis recommended • For protozoal infections: Fecal waste disposal in a clean environment, treating drinking water	• For helminth infections, high-risk groups should be screened and treated. Sanitary disposal of human waste is also recommended. • Piperacillin-tazobactam or Meropenem administration, percutaneous or surgical aspiration of massive liver abscesses, metronidazole or tinidazole followed by diiodohydroxyquinoline/iodoquinol for patients with invasive colitis are all treatments for protozoal infections.	[6]