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Review

Preventing and Managing Infections in Patients with Sickle Cell Disease

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Abstract

Sickle cell disease (SCD) is a genetic disorder that causes abnormal hemoglobin, resulting in red blood cell sickling and increased vulnerability to infections. Environmental factors like hypoxia, cold, and dehydration can trigger sickling episodes, exacerbating the condition. Infection is a major cause of morbidity and mortality in SCD patients, particularly in low-income regions with limited access to healthcare. Impaired splenic function and immune deficiencies increase the risk of bacterial infections such as Streptococcus pneumoniae and Salmonella. Preventive measures like vaccinations and antibiotic prophylaxis have reduced infection-related complications, particularly in high-income countries. Despite advances in SCD care, such as hydroxyurea use and early screening programs, infection remains a serious issue, especially in resource-poor settings. Proactive infection prevention, early diagnosis, and comprehensive management are crucial to improving the life expectancy and quality of life for SCD patients globally. Ongoing research is essential to further enhance infection prevention strategies for this vulnerable population.

Keywords: *sickle cell disease, infections, sickling, vaccinations, antibiotic prophylaxis, morbidity, mortality, prevention*

Introduction

Sickle cell disease (SCD) includes genetic disorders characterized by abnormal hemoglobin, leading to intermittent sickling of red blood cells (RBCs) and various clinical symptoms. The genetic mutation responsible is a single nucleotide substitution (GTG for GAG) in the b-globin gene on chromosome 11, replacing glutamic acid with valine, forming hemoglobin S (HbS) (1). Normal hemoglobin (HbA) consists of two a-globin and two b-globin chains, but HbS undergoes polymerization during deoxygenation, causing RBCs to form sickle shapes (2). These sickled RBCs become rigid and obstruct small blood vessels, impairing blood flow and leading to ischemia and infarction. Environmental factors such as hypoxia, acidosis, cold, and dehydration can trigger sickling episodes, as can infections. Homozygous individuals (HbSS) suffer from sickle cell anemia, while compound heterozygotes (HbS with HbC, D, OArab, or b-thalassemia) show variable symptoms. Carriers (HbAS) typically do not experience severe effects, though sickling can occur in extreme conditions (1).

Hemolysis and vaso-occlusion are symptoms of SCD. Ischemia, discomfort, and long-term organ damage result from sickled RBCs, leukocytes, and platelets adhering to the vascular endothelium and blocking blood flow. Hemolysis leads to chronic anemia (Hb 6–8 g/dl), contributing to cardiomegaly and poor growth in children. Free hemoglobin from RBC destruction depletes nitric oxide (NO), exacerbating vascular damage (3). Despite therapeutic advances, SCD still results in significant morbidity and mortality.

An estimated 300,000 infants are born each year with SCD, primarily in sub-Saharan Africa, although the disorder is seen throughout the world (4, 5). About 100,000 persons in the US have sickle cell disease (SCD), which affects 1 in 2,500 live births (6). However, just 10% of people with SCD worldwide live in high-income nations (HICs) (7). With an estimated 12–15 million of the 25 million SCD sufferers worldwide residing there, Africa suffers the greatest burden. 75% of kids with SCD are born in Africa, where the under-5 mortality rate is more than 50%. Childhood mortality from SCD is highest between the ages of six months and three years (7, 8).

This growing burden presents a significant global health challenge, affecting both high- and low-income countries (5). In high-income regions, improved life expectancy has been driven by advances in screening, antibiotic prophylaxis, and hydroxyurea therapy, which have reduced childhood mortality (9). Hydroxyurea, the only approved pharmacological treatment for SCD, increases fetal hemoglobin (HbF), reducing sickling and the frequency of painful crises (10). It also reduces leukocyte and platelet counts, improving blood flow and minimizing vaso-occlusive complications. However, its use remains limited, especially in lower-income regions (11). New therapies aimed at HbF induction are under development. While survival rates for infants with SCD have improved in high-income countries, patients in low-income regions face significant barriers to care (12). Africans with SCD have a life expectancy of less than 20 years, and the mortality rate for children under five is 90% (13). Increased infection susceptibility and poor healthcare infrastructure contribute to this severe disease course. Environmental factors further worsen outcomes in low-income countries (14).

Methodology

This study is based on a comprehensive literature search conducted on 18 October 2024, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed preventing and managing infections in patients with sickle cell disease. There were no restrictions on date, language, participant age, or type of publication.

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Discussion

Interactions between SCD and infections are bidirectional, as SCD increases susceptibility to infections, while infections exacerbate SCD-specific pathophysiological changes. Most SCD patients live in low-income countries with high infection prevalence, creating an environment conducive to infections. Necrotic bone serving as infection foci is one mechanism associating infection to red cell sickling and vaso-occlusive crises. *Salmonella* is the most prevalent pathogen in SCD-related osteomyelitis, followed by *Staphylococcus aureus* and Gram-negative enteric bacteria (14). Microvascular bowel infarctions facilitate bacterial entry into the bloodstream, with *Edwardsiella tarda* also showing increased incidence (15). SCD patients face elevated risks of respiratory infections caused by *Mycoplasma* and *Chlamydia* (16). Infections are also a common trigger for crises in SCD, as they elevate leukocyte adhesion, inflammatory cytokines, and oxidative stress, contributing to microvascular occlusion and further sickling. Dehydration from infection-related symptoms like fever, vomiting, and diarrhea increases HbS concentration, accelerating polymerization and irreversible membrane damage (14).

Factors Influencing Infection Susceptibility in Sickle Cell Disease

Environmental factors significantly contribute to infection susceptibility in individuals with SCD, as they affect various physiological and external conditions that influence the course of the disease. Environmental determinants such as climate, air quality, housing conditions, socio-economic status, and physical activity levels all play crucial roles in shaping health outcomes for SCD patients (14). Cold weather has been linked to vasoconstriction, which can increase blood viscosity and cause higher deoxygenation rates, ultimately worsening sickle cell pain and triggering infections (17). However, studies have produced mixed results regarding the relationship between cold weather and acute pain crises, with some finding a connection, while others have not supported these findings (14). Similarly, in tropical regions, factors such as high wind speeds have been associated with increased hospital admissions for pain management, and extreme humidity has been correlated with higher rates of hospitalization due to complications from SCD (18). Additionally, environmental pollutants like air pollution and tobacco smoke can exacerbate infection risks through mechanisms involving inflammation, oxidative stress, and endothelial dysfunction, while socio-economic factors, such as poverty, further worsen the susceptibility to infection by limiting access to adequate healthcare and nutrition. Poor nutrition and deficiencies in essential micronutrients, like zinc, compromise immune function, making individuals more prone to infections. Zinc supplementation, in particular, has been shown to improve immune response and reduce infection rates in SCD patients (14).

Impaired splenic function is a major factor contributing to the heightened susceptibility to bacterial infections in SCD. The spleen is a critical organ in the body's immune system, responsible for filtering intravascular pathogens, defective red blood cells, and other foreign particles, while also playing a central role in antibody production. In healthy individuals, the spleen enables the immune system to recognize and mount a defense against polysaccharide antigens, primarily through the production of IgM antibodies and memory B cells. However, in patients with SCD, the spleen often becomes progressively damaged due to repeated episodes of ischemia, eventually leading to asplenia, or a non-functioning spleen, which severely impairs the body's ability to clear encapsulated bacteria (19). *Streptococcus pneumoniae* and other encapsulated germs depend on the spleen for efficient removal from the bloodstream, making this asplenic state a greater risk. Individuals with SCD are therefore at much higher risk of developing severe bacterial infections, which can be life-threatening if not treated promptly. Deficiencies in complement activation further exacerbate this risk, as the complement system plays an essential role in the opsonization and destruction of pathogens (20).

Early research suggested that some patients with SCD exhibit defects in the alternative complement pathway, particularly in factor B levels, which may

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reduce the body's ability to fight off bacterial infections (21). Although these findings need further validation, they underscore the multifaceted challenges SCD patients face in managing infections (22). The clinical relevance of reduced leukocyte function, including diminished neutrophil killing capacity, has also been linked to increased disease severity in SCD, though this relationship has not been consistently observed (23).

Genetic factors further complicate the picture of infection susceptibility in SCD, as disease severity and infection risk vary widely among patients with the same genetic mutation. This variability suggests a multigenic phenotype, where several genes likely influence the pathophysiology of SCD, including susceptibility to infections. Specific polymorphisms in immune-related genes, such as HLA II, Fc receptors, mannose-binding lectin, and insulin-like growth factor 1 receptor (IGF1-R), have been associated with a higher risk of infection. These genetic differences may help explain why some individuals with SCD experience frequent and severe crises, while others lead relatively normal lives despite carrying the same underlying mutation (1). Additionally, mechanical factors associated with SCD, such as bone marrow expansion and sluggish blood circulation, create an environment that fosters infections, particularly in tissues vulnerable to vaso-occlusion and infarction. For example, SCD patients are at an increased risk of developing osteomyelitis, an infection of the bone, due to ischemia and necrosis in the bone marrow. *Salmonella* is the most common pathogen responsible for osteomyelitis in SCD patients, followed by Staphylococcus aureus and Gram-negative enteric bacteria (24). Infections such as acute chest syndrome are also prevalent, especially during respiratory infections caused by pathogens like *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (1). Furthermore, iatrogenic infections, including those acquired during blood transfusions and catheter use, pose additional risks for SCD patients, especially those undergoing chronic transfusion therapy for the prevention of stroke or the treatment of other complications (25). While improved screening methods have reduced the transmission of blood-borne pathogens such as hepatitis B, hepatitis C, and HIV in developed countries, transfusion-related infections remain a significant concern in regions with less stringent screening protocols (26).

Individuals with SCD are particularly vulnerable to a wide range of infections due to their compromised immune systems and other disease-related factors. Understanding the types of pathogens and their associated risks is critical for managing and preventing severe complications. Infections can trigger or exacerbate conditions such as septicemia, acute chest syndrome, and aplastic crisis, leading to high morbidity and mortality rates in these patients **(Table 1)** (27).

Prevention and prophylaxis of Sickle Cell Disease

Prophylaxis against infections has been instrumental in lowering the rates of infectious complications and mortality in individuals with SCD. This success is largely attributed to advancements in antibiotic prophylaxis, immunization, and the prompt use of antibiotics during febrile episodes. Early identification of infants through perinatal screening for SCD is essential to ensure they can benefit from these preventive strategies (27). Prior to the use of penicillin for prophylaxis, the incidence of invasive pneumococcal disease was about six cases per 100 patient-years, with the highest incidence in children younger than three years. The introduction of pneumococcal polysaccharide vaccines has greatly decreased the likelihood of invasive pneumococcal disease, particularly in children receiving daily prophylactic penicillin (28). While the decision to continue penicillin prophylaxis into adulthood remains debated, most pediatric hematologists advocate for stopping prophylaxis around the age of five. However, the role of penicillin in patients with HbSC, HbS-β+ thalassemia, and other compound heterozygotes is still under discussion (27).

According to guidelines from the National Heart, Lung, and Blood Institute, children with homozygous SCD (Hb SS) should receive oral penicillin prophylaxis. The recommended dose is 125 mg for children younger than three years and

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250 mg for those aged three and older, administered twice daily until the age of five (29). Prophylaxis can be discontinued at age five if the patient has no history of invasive pneumococcal disease, has not had a splenectomy, and has been adequately vaccinated against pneumococcus. The introduction of the heptavalent pneumococcal conjugate vaccine (PCV7) led to a 70% decline in invasive pneumococcal disease rates, and the newer PCV13 vaccine has further reduced the incidence of severe pneumococcal infections (27).

Table 1. Infectious Pathogens and Their Impact on Sickle Cell Disease (27)

Infection Type	Pathogens	Key Points
Bacterial	S. pneumoniae, N. meningitidis, H. influenzae, E. coli	Pre-vaccination pathogens. Bacteremia 10–32% of febrile cases. Septicemia mortality 35–50% in infants.
	Salmonella, S. aureus, Gram-negative bacilli	Common in osteomyelitis (0.5–16%). UTIs (6–26%) can lead to septicemia.
	S. pneumoniae (Pneumonia)	Majorcause of pneumonia in children. Triggers acute chest syndrome in 50% of cases.
Viral	Influenza, Rhinovirus	Cause acute chest syndrome, aplastic crisis.
	Parvovirus B19, Hepatitis B/C, EBV, HIV	Parvovirus causes aplastic crisis. HIV increases bacterial infection risk.
	Dengue	Increased risk of capillary leakage, hypovolemia.
Parasitic	Malaria	SCD patients face higher mortality from malaria.
	Intestinal parasites	Worsen anemia, increase need for transfusions.
	Schistosomiasis	Exacerbates anemia, raises UTI risk.
Mycobacterial	M. tuberculosis	Common in endemic regions. Standard treatment is effective.

Standard protocol now includes beginning daily penicillin prophylaxis at two months of age and completing the pneumococcal vaccine series, which involves both PCV13 and the pneumococcal 23-valent vaccine, by age five. Some centers recommend booster doses of the pneumococcal polysaccharide vaccine every five years, though this practice is not yet supported by formal evidence-based guidelines (30). Additionally, children with SCD should receive vaccines against meningococcal disease and annual influenza vaccinations. Fever of 38.5°C or higher is considered a medical emergency in SCD patients due to the risk of invasive pneumococcal disease. Febrile episodes in these patients require urgent evaluation, including physical examination, complete blood count, and blood cultures (29).

While hospitalization is sometimes required, many SCD patients presenting with fever but without high-risk factors—such as an extremely elevated white blood cell count or fever over 40°C—can be treated as outpatients. They can receive a single dose of an empiric anti-pneumococcal antibiotic like ceftriaxone, which also covers Gram-negative enteric bacteria. It's essential to rule out other SCD-related complications, such as acute chest syndrome. Since the average time for a positive blood culture result in SCD patients is under 24

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hours, one dose of ceftriaxone is often adequate for outpatient care (31).

In regions with endemic infections such as malaria and dengue, additional prophylaxis measures are needed. Malaria chemoprophylaxis is essential for SCD patients in malaria-endemic areas as it reduces the frequency of crises and decreases mortality. Long-term malaria prophylaxis has been shown to lower the rate of sickle cell crises, hospitalizations, and anemia severity, although further studies are required to compare antimalarial drugs and assess potential long-term side effects (27). Although little is known about the impact of antimalarial drug resistance on its efficacy in SCD patients, it remains an area of active research (32).

In addition to malaria, SCD patients traveling to areas where typhoid fever is endemic should receive prophylaxis against *Salmonella typhi*. Two vaccines are available: the oral live-attenuated Ty21a and the inactivated Vi capsular polysaccharide vaccine for individuals over two years old. Although the effectiveness of these vaccines in SCD patients is not entirely clear, both are permitted, as SCD patients are considered to have reduced immune function due to asplenia. The oral vaccine is preferred for those who meet the age requirement, as it generally causes fewer side effects compared to the injectable version (27).

The Centers for Disease Control (CDC) provides guidelines for travelers with SCD, which include recommendations for vaccinations and prophylaxis based on the region of travel, local outbreaks, and the patient's age and immune status. These guidelines are important for healthcare providers managing patients who may be exposed to endemic infections. In developed countries, where newborn screening and preventive measures like penicillin prophylaxis and vaccinations are routinely implemented, the rate of bacteremia in SCD patients has decreased to less than 1% (33). In resource-limited areas, key priorities should focus on identifying the bacterial pathogens most significant to SCD patients in specific regions, establishing comprehensive perinatal screening for SCD, and creating vaccination and antibiotic prophylaxis programs that are specifically adapted to the bacterial epidemiology of the region (27).

Conclusion

Preventing and managing infections in SCD is crucial for reducing morbidity and mortality, particularly in low-resource settings. Prophylaxis, early screening, and vaccinations significantly improve outcomes. Ongoing research and customized preventive strategies are crucial to addressing infection risks and enhancing the quality of life for individuals with SCD globally.

Disclosure

Conflict of interest

There is no conflict of interest.

Funding

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Ethical Consideration

Not applicable.

Data availability

Data that supports the findings of this study are embedded within the manuscript which is based on a comprehensive literature search conducted on October 2024, in the Medline and Cochrane databases.

Author Contribution

The authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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