Review

Infection and Potential Challenge of Childhood Mortality in Sickle Cell Disease: A Comprehensive Review of the Literature from a Global Perspective

Tarun Sahu [1,†] , **Babita Pande** [1,†] , **Henu Kumar Verma** [2,*] , **L V K S Bhaskar** [3] , **Meenakshi Sinha** [1], **Ramanjan Sinha** [1] **and Pasupuleti Visweswara Rao** [4,5]

1 Department of Physiology, All India Institute of Medical Science, Raipur 492001, India; tarun.sahu.50@gmail.com (T.S.); babitatime2014@gmail.com (B.P.); sinham66@aiimsraipur.edu.in (M.S.); rsinha45@aiimsraipur.edu.in (R.S.)
2 Department of Immunopathology, Institute of Lungs Health and Immunity Comprehensive Pneumology Center, 85764 Munich, Germany
3 Department of Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, India; lvksbhaskar@gmail.com
4 Department of Biomedical Sciences and Therapeutics, Faculty of Medicine & Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu 44800, Sabah, Malaysia; visweswararao@reva.edu.in
5 Department of Biochemistry, Faculty of Medicine and Health Sciences, Abdurrab University, Pekanbaru 28291, Riau, Indonesia
* Correspondence: henukumar.verma@helmholtz-munich.de
† These authors contributed equally to this work.

Abstract: Sickle cell disease (SCD) is a complex genetic disorder associated with multiple clinical manifestations, including increased susceptibility to bacterial and viral infections. This review article presents a comprehensive analysis of the current literature obtained from various online databases focusing on the relationship between SCD and infections caused by specific pathogens, such as pneumonia- and influenza-causing pathogens, *Escherichia coli*, *Staphylococcus aureus*, parvovirus, and hepatitis viruses. We discuss the underlying mechanisms that contribute to the increased susceptibility of individuals with SCD to these infections, primarily related to the pathophysiology of variant hemoglobin (HbSS) and its impact on vascular occlusion, hemolysis, functional asplenia, and immune deficiency. Moreover, we highlight the significant burden of infections on SCD patients, particularly children under five years of age, where they are the leading cause of morbidity and mortality. Additionally, we address the challenges faced in attempts for reducing the global mortality rate associated with SCD, particularly in low-income countries, where factors such as increased pathogen exposure, co-morbidities like malnutrition, lower vaccination rates, and limited healthcare facilities contribute to the high disease burden. This review emphasizes the need for targeted interventions, improved healthcare access, vaccination programs, and infection prevention strategies to alleviate the impact of infections on individuals with SCD and reduce the global mortality rates associated with the disease.

Keywords: sickle cell disease; infection; bacteria; virus; molecular mechanism; children therapeutics

1. Introduction

Sickle cell disease (SCD) is caused by a single amino acid substitution (Glu > Val) at codon six at the globin gene, which results in variant hemoglobin formation (HbSS). This causes an increase in viscosity and adhesion to vascular walls, resulting in obstructing the blood flow in small capillaries [1]. This primary pathophysiological condition has several clinical manifestations, such as vaso-occlusive crisis (VOC), splenomegaly, acute chest syndrome (ACS), ocular manifestation, hepatomegaly, pulmonary hypertension, leg ulcers, chronic kidney disease (CKD), and stroke, which leads to early mortality [2–5]. However, in the current scenario, hydroxyurea (HU) is the only SCD drug approved by the Food and

Drug Administration (FDA) to increase fetal hemoglobin (HbF) levels [6]. Universally, it is found that more than 300,000 children are born with SCD each year, of which two-thirds are from Africa, while Nigeria, India, and the Democratic Republic of Congo bear half the global burden of SCD. It is expected that this number will rise to about 400,000 by 2050 [7].

The phenotypic manifestation of the disease is still poorly understood. However, environmental factors, including climate and air quality, infections, fetal hemoglobin levels, and other genetic factors, play a vital role in the progression of the disease [8,9]. The severity of the disease in pediatric SCD patients, particularly those under the age of five years, is increased for various reasons, including rapid sequestration of red blood cells in the spleen, failure of opsonization, and an inability to deal with infective encapsulated microorganisms after infection [10,11]. As a result, in children with SCD, infection is the second leading cause of death in their first ten years.

SCD patients in sub-Saharan Africa and the Eastern Mediterranean have a high infection rate, with obtrusive pneumococcal infection being the most common [12]. The global reports suggest implementing an effective management and systemic newborn screening (NBS) program is the first logical step in preventing disease [12]. The initial neonatal screening and the arrangement of immunization and prophylactic antimicrobial agents improve the quality of care for SCD patients, resulting in a significant decrease in mortality. However, in this review article, we discussed several aspects of infections in SCD children, the underlying mechanisms for susceptibility to specific pathogens, and how infection affects SCD outcomes. We also highlight the difficulties in reducing the global burden of SCD mortality.

2. Materials and Methods

Electronic databases, including PubMed, Web of Science, Google Scholar, and EMBASE were utilized to retrieve relevant published articles. A comprehensive search strategy was employed by combining keywords, including "sickle cell disease"/"sickle cell anemia", AND "hemoglobinopathy", "vaso-occlusive crisis", "pathophysiology", "clinical manifestations", "bacterial infections", "viral infections", "parasitic infections", "sepsis", "pneumococcal infections", "streptococcus infections/complications", "pneumonia", "osteomyelitis", "meningitis", bacteremia, "sickle cell" AND "COVID-19, prevention, therapeutics, and management". Furthermore, to identify additional pertinent studies, references from relevant original papers and review articles were examined.

Keywords searched		
"sickle cell disease"/"sickle cell anemia"	AND	"hemoglobinopathy", "vaso-occlusive crisis", "pathophysiology", "clinical manifestations", "bacterial infections", "viral infections", "parasitic infections", "sepsis", "pneumococcal infections", "streptococcus infections/complications", "pneumonia", "osteomyelitis", "meningitis", "bacteremia"
"sickle cell"	AND	"COVID-19, prevention, therapeutics, and management"

3. Results and Discussion

3.1. Immune Dysfunction and Susceptibility to Infection

In patients with SCD, the primary complications often arise from infections. The exact reason behind susceptibility to infections is complicated. A significant contributing factor is the impaired functioning of the spleen. SCD has been associated with abnormalities in processes such as opsonization, the alternate complement pathway, antibody production, leucocyte function, and cell-mediated immunity.

Individuals with SCD exhibit deficiencies in their innate immune system, primarily attributed to reduced splenic function, making them more susceptible to infections caused by encapsulated bacteria, and the compromised innate immune response stems from malfunctions in elements like chemotaxis, migration, and scavenging due to faulty neutrophils, alongside decreased splenic phagocytic filtration and a diminished opsonization capabil-

ity [11]. Furthermore, the adaptive immune system in SCD is compromised, characterized by a reduced production of memory B cells and crucial IgM components, essential for the humoral immune system. This weakened immunity hinders the ability to combat viral infections, thereby worsening the condition in SCD patients, and the impact of infections contributes to multi-organ dysfunction [8].

3.2. Splenic Dysfunction

The spleen is primarily involved in the filtration of foreign microorganisms and the support of innate and adaptive immune functions. It serves various vital functions in immune response and plays a critical role in increasing vulnerability to most SCD patients' infections. The spleen helps two essential tasks prevent bloodstream bacterial infections. First, it is a phagocytic filter that removes bacteria from the bloodstream. Second, the spleen hosts leucocytes, which produce an antibody response to polysaccharide antigens [13]. Still, most infections are caused by SCD complications, such as acidosis, hypoxia, and dehydration, which activate or exaggerate the sickle cell crises and cause vaso-occlusion and ischemia, ultimately harming the structure and function of the spleen [14].

Individuals with splenectomy and individuals with non- or partially functioning spleens (hypo or asplenism), as in SCD, are more vulnerable to infections. Hyposplenic and asplenic individuals lack IgM memory B cells (as stated above, the spleen is a major site of their generation or function). Thus, it cannot provide a rapid, precise response to encapsulated species of microorganisms, particularly *Haemophilus influenzae* type b (Hib), salmonellae, and pneumococcal infections [15]. Local infections can easily become systemic, which, combined with the loss of spleen filtering function, can contribute to the development of severe sepsis. The risk of infection in children under the age of five with SCD is nearly thirty to a hundred times higher than in healthy children, implying that SCD children are more vulnerable to invasive pneumococcal disease (IPD), including pneumonia, meningitis, and septicemia [16]. In addition, patients with SCD have a 25 times higher risk of salmonella infections, particularly in older children and adults [17]. The factors associated with increased SCD infections may be related or unrelated to the immune system. Few infections can occur as a result of treatment.

3.3. Opsonization

Splenic opsonization is compromised in SCD conditions due to a lack of production of the immunoglobins and opsonins required for bacterial destruction. The effective opsonization process is dependent on a complement cascade, which is activated by both classical and alternative pathways and destroys infectious microorganisms by creating holes in their cell membranes [18]. Lack of splenic IgM leads to decreased opsonization and impaired activation of the classical pathway. Another opsonin, tuftsin, formed in the spleen and required to activate cell-mediated immunity, is reduced in SCD patients, indicating that the spleen is involved in their synthesis [19]. Furthermore, a lack of C3b-binding protease enhances the alternative complement pathway, possibly due to depletion from clearing sickle shaped RBC caused by intravascular hemolysis, and ultimately reduces the alternative complement pathway's immune function [20,21].

3.4. Lymphocytes

SCD patients are more susceptible to unusual pathogens, implying that other immune system defects compromise their immune systems. SCD reduces the production and function of B and T lymphocyte cells, resulting in impaired memory B-cell and anti-polysaccharide antibody formation [22–24]. Also, the IgM antibody response to an influenza virus vaccine is impaired [24]. There are also lower T-cell subsets CD4+ and CD8+ in SCD patients, which affect their divergence into mature lymphocytes [25]. Therefore, there is decreased production in both the Th1 (IFN-gamma, IL-2, and TNF-beta) and Th2 (IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13) responses of CD4+ T-helper cells in SCD [26].

3.5. Nutritional Deficiencies

Nutritional deficiencies also have a major impact on SCD children's immune systems. SCD patients have macro-and micronutrient deficiencies due to pathways that include reduced calorie consumption, increased basal metabolic rate (BMR), increased RBC synthesis, increased protein turnover, dysregulated inflammatory response, and high myocardial energy requirements. Micronutrient deficiencies are associated with increased susceptibility to infection and a higher rate of SCD complications [27]. Low plasma zinc levels in malnourished children usually result in immune dysfunction. IL-2 is required for cell-mediated immunity maturation, and zinc deficiency causes lymphopenia, a decreased production of IL-2, which impairs the coordination of the innate and adaptive immune systems. Zinc deficiency is caused by insufficient food consumption, high protein turnover, and increased loss from the kidney due to insufficient reabsorption. Zinc supplementation improves somatic development in SCD children, and vitamins A, B, and magnesium have been shown to reduce inflammation, vaso-occlusive crisis, and hospitalizations [28–32].

3.6. Hereditary Influences

Despite having the same genetic defect, the severity of SCD varies widely among individuals because not all patients have identical pleiotropic genes. Some carriers have mutated genes, whichcan either improve or worsen the phenotype. This suggests that the phenotype of SCD is multigenic. Some other genes unrelated to the globin locus participate in relevant pathological events (rapid destruction of sickle cells, dense cell formation, endothelial adhesion) controlled by many, known as pleiotropic or secondary effector genes [33]. Polymorphisms in various immune-related genes have been proposed as a factor for increased vulnerability to infection in SCD patients. Previous findings show direct involvement of the HLA class II polymorphism in developing primary infections in SCD [34]. The increased risk of bacteremia may be controlled by the mannose-binding lectin receptor, Fc receptor, beta-S gene cluster haplotypes, IGF1R, and the TGF-beta/bone morphogenetic protein (BMP) pathway [35–38].

3.7. Mechanical Factors

Several mechanical factors may also play a role in a wide range of infections in SCD patients. Environmental factors can contribute to a variety of infections in SCD. The leading cause of respiratory infection in SCD is air pollution. Tobacco smoke exposure increases the risk of sickle cell crises in children with SCD due to chronic tissue hypoxia, vascular endothelial cell damage, and thrombus formation.

Furthermore, tobacco smoke may indirectly exacerbate asthma and acute chest syndrome in patients with SCD [39,40]. SCD patients are also predisposed to a variety of iatrogenic infections as a result of therapeutic interventions. Some of the complications treated by blood transfusion include vaso-occlusive crisis, splenic sequestration, acute chest syndrome, priapism, and strokes. Blood transfusions without pathogen screening can increase the risk of blood-borne infections, most notably hepatitis B and C, HIV, cytomegalovirus (CMV), and B19 parvovirus. Patients who are iron-overloaded and on deferoxamine medication due to frequent transfusions are especially vulnerable to *Yersinia enterocolitica* [41]. Patients with SCD who have a venous catheter in place for long-term blood transfusions are also at risk of bloodstream infections (BSI). Despite adequate antibiotic therapy, BSI, such as *Staphylococcus aureus* and Pneumococci, is hospital-acquired and primarily associated with venous catheters. These patients are at a high risk of developing an associated bone–joint infection if they are not adequately treated [42].

3.8. Molecular Mechanism of Clinical Manifestations in SCD

SCD patients are susceptible to infections due to a variety of immunological abnormalities and exposure to infectious agents. Pathophysiological mechanisms of the disease can explain the disease's role in stimulating immune dysfunction. The clinical manifestations of infection in SCD are primarily vaso-occlusion, which causes endothelial dysfunction and

hemolysis. The detailed molecular mechanism involved in the clinical manifestations of SCD is depicted in Figure 1.
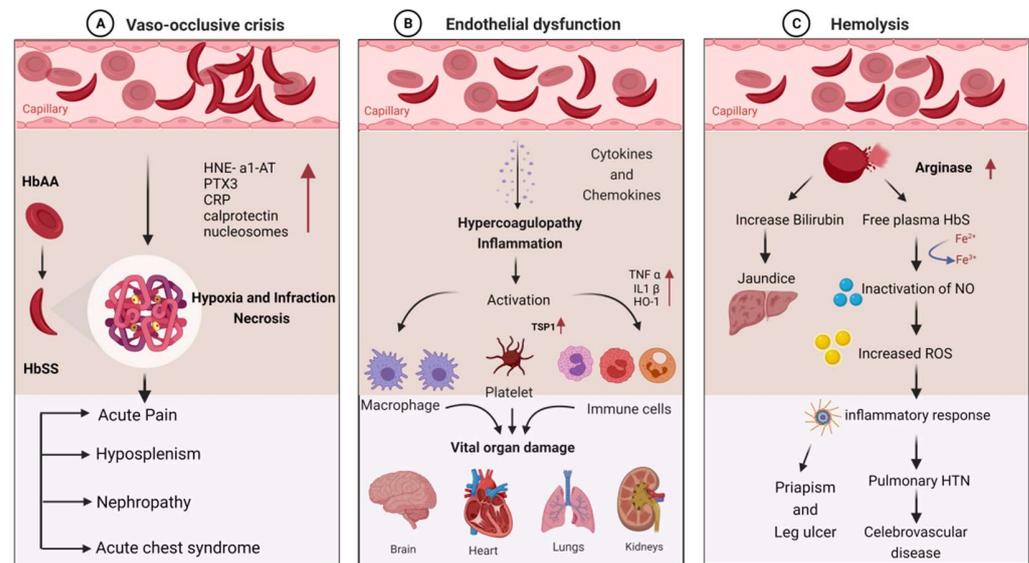

Figure 1. Molecular mechanism involved in the clinical manifestations of SCD due to infections: (**A**) vaso-occlusive crisis; (**B**) endothelial dysfunction; (**C**) hemolysis.

Hematocrit, plasma viscosity, and erythrocyte deformability are some factors that affect blood rheology. Sickled RBCs become mechanically trapped in the microcirculation, promoting adhesive events among blood cells and resulting in chronic vaso-occlusion, causing frequent episodes of pain, hemolytic anemia, organ damage, and premature death [43,44]. Sickled RBCs also promote the exposure of adhesion molecules and binding motifs that are not generally found on RBCs' outer membranes, such as phosphatidyl serine (PS), basal cell adhesion molecule-1 (B-CAM1), integrin-associated protein (IAP), and intercellular-adhesion-molecule-4 (ICAM-4). Sickled RBCs also have an integrin complex on their surface, which binds to fibronectin and vascular-cell adhesion molecule 1 (VCAM1), expressed on endothelial cells' membrane and activated by inflammatory cytokines like tumor necrosis factor-alpha. C-reactive protein (CRP) is generated in response to interleukin-6 and pentraxin 3 (PTX3), generated mainly by neutrophils and endothelial cells as a result of an inflammatory response [45–47]. Thrombospondin, secreted by activated platelets, binds to endothelial cells and sickled RBC via CD36 and sulfated glycans found only on sickled RBC.

The interaction of sickled RBC with vascular endothelium may result in the formation of oxygen radicals by the endothelial cell and the transcription factor NF-kB by oxidants. When NF-kB is activated, the transcription of various genes of adhesion molecules, such as E- and P-selectin, VCAM-1, and ICAM-1, on the endothelial surface is increased [2]. It also increases the expression of major leukocyte chemo-attractants, such as interleukin-8 (IL-8) on endothelial cells [1,48]. Neutrophil-derived azurophilic protein elastase, with its inhibitor a1-antitrypsin (HNE-a1-AT), and neutrophil cytosolic protein calprotectin levels are increased with the activation of neutrophils. The inflammatory environment during VOC may also promote neutrophil, monocyte, and platelet activation, which increases their adhesion to each other and activated endothelial cells. These activated neutrophils, monocytes, and platelets do not act against pathogens but rather contribute to VOCs and act as sources of oxidative stress, impairing the immune response [49]. Activated neutrophils form neutrophil extracellular traps (NETs), and during NET formation, nucleosomes are squeezed out of the neutrophils, resulting in higher nucleosome levels during VOC [50,51]. Vaso-occlusion, on the other hand, contributes to ischemia–reperfusion injury, promoting chronic inflammation in SCD.

Hemolysis causes Hb to oxidize, resulting in the formation of heme and its oxidized form. The Fe^{3+} and Fe^{4+} states of hemoglobin formed in SCD are highly reactive in terms of encouraging oxidation. Hemolysis also results in red cell microparticles, which can deliver toxic heme to endothelial cells [52,53]. These hemolysis products are thought to be erythrocyte danger-associated molecular patterns (eDAMPs), which trigger innate immune responses and may play a role in sickle cell inflammation [54,55]. Hemin is also a potent TLR4 agonist, which contributes to a proinflammatory and procoagulant state in SCD. Because of the increased production of placental growth factor (PlGF) resulting from ischemia–reperfusion injury, monocytes are activated in response to PlGF, secreting more TNF-a, IL-1, and other chemokines. These increased oxidant production and leukocyte adhesion to the endothelium, followed by extravasation into the tissues and, finally, tissue damage [56]. Increased hemolysis and reperfusion promote chronic hypoxia, ROS production, microvasculature dysfunction, innate and adaptive immune response activation, and cell death, all of which contribute to ischemia–reperfusion injury. ROS-dependent degradation of cellular proteins, lipids, DNA, and ribonucleic acids triggers cell death programs, such as apoptosis, necrosis, and autophagy [57,58].

3.9. Infectious Complications Associated with SCD

Researchers previously identified bacterial infections as the leading cause of morbidity and mortality in SCD patients, and children are the most vulnerable age group [59–62]. SCD increases susceptibility to various microbial, viral, parasitic, and Protozoan infections (Figure 2). Bacteremia/sepsis is caused by both Gram-positive (*S. pneumonia* and *S. aureus*) and Gram-negative (*E. coli*, *Klebsiella,* and *Bacteroides*) bacteria, which is the most common infection reported [63]. The infections become more severe during severe anemia and recurrent VOC. The prevalence, susceptibility, and severity of the effect on disease depend on the age group. Children are more susceptible to sepsis and pneumococcal infection [64]. However, adults in their forties and fifties commonly report organ-specific infections, including pyelonephritis and osteomyelitis. Some of the infections that increase the risk of mortality are as follows.
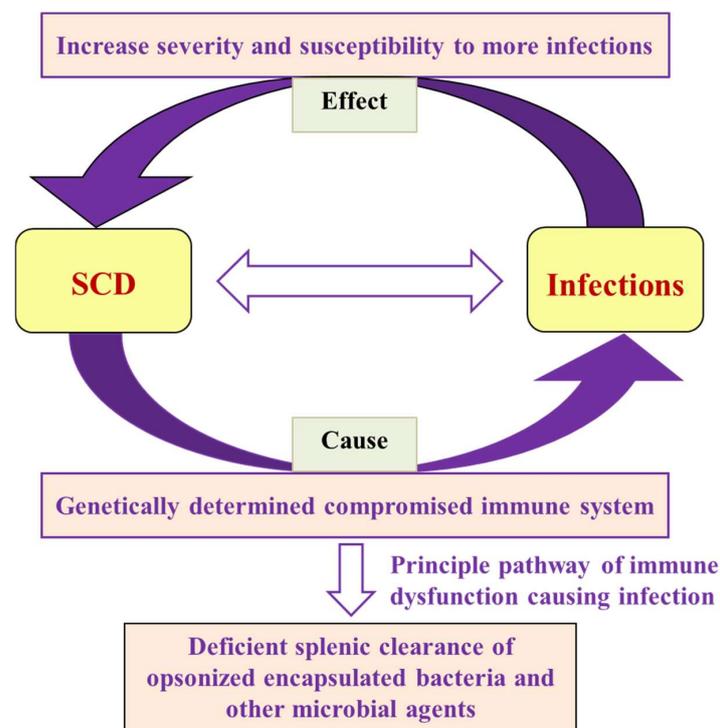

Figure 2. Flow chart showing the interrelationship of SCD and infections in terms of cause and effect, along with the failure of the primary mechanism that leads to microbial and parasitic infections.

3.10. Bacterial Infections

3.10.1. Bacteremia, Sepsis, and Pneumonia

Bacteremia and sepsis are common complications of SCD. *Streptococcus pneumonia*, *Neisseria meningitides*, *Haemophilus influenza*, and *Escherichia coli* cause sepsis [65]. *Klebsiella pneumonia* and *Staphylococcus aureus* are two other bacteria that can cause bacteremia and septicemia [66]. Salmonella species and *Pantoea agglomerans* enteric Gram-negative bacteria also negatively impact SCD patients [67,68]. An extensive data analysis of 550 SCD patients shows that the use of catheters during red cell exchange/transfusion increased the risk of bacteremia or thrombosis [69]. Cannas et al. noticed the rapid progression of infection and a high mortality rate in SCD children with bacteremia/sepsis or meningitis infections, irrespective of treatment with penicillin sodium ampicillin trihydrate [70].

Children with SCD have immune dysfunctions that cause severe sepsis symptoms, which is less common in normal children [71]. Sickling infants are more susceptible to *Streptococcus pneumonia* infections due to several factors, including the interference of antibody production, opsonophagocytosis, and functional asplenia, as well as defective splenic clearance [72]. On the other hand, children and adults are more susceptible to *S. pneumonia* infections due to a lack of IgG and IgM antibody response and impairments in splenic complement and opsonophagocytic functions [65]. Penicillin prophylaxis and vaccination against bacteremia are preventive measures for infections that have reduced childhood mortality [73]. Pneumonia is the most common chronic infection that causes death in children worldwide and is caused by encapsulated microbial species, the most common of which is *Mycoplasma pneumoniae*. Studies show that *diplococcus pneumonia*, salmonella species, and *Hemophilus influenza* cause more illness in children than their normal counterparts [74–76].

Among 2444 SCD patients, Yee et al. has shown that children up to five years of age have been more infected with *S. pneumoniae* and *H. influenza* [77]. SCD patients with bacterial pneumonia developed ACS, which causes pulmonary infarction in the young age group and emboli or thrombosis in older patients [78,79]. Pneumococcal polysaccharide vaccine 23 (PPSV23) was observed to be ineffective against some strain *S. pneumonia* in an adult SCD patient with functional asplenia and reduced IgG [80].

3.10.2. Acute Chest Syndrome (ACS)

Acute chest syndrome is one of the major clinical manifestations of SCD, leading to death. Primarily bacterial and viral infections cause ACS due to functional asplenia. Children under five years of age with SCD have been reported with high mortality rates because of *Streptococcus pneumonia* infection, responsible for ACS [81]. *S. pneumonia* is also a causative organism for severe anemia. It causes inflammation of the lungs by migrating from the upper respiratory tract to the lower respiratory tract [82].

3.10.3. Meningitis

Recently Chenou et al. observed that SCD patients are 300 times more likely to develop bacterial meningitis than the normal population, and 10% of affected children die due to the infection generated by meningitis and pneumococcus [83]. Previous research found that meningitis in SCD patients caused by various bacteria, including *H. influenzae*, *H. meningitis*, and *E. coli* [84], and *Streptococcus pneumonia*, was responsible for 70% of bacterial meningitis cases in SCD children, while *H. influenza* was responsible for 80% [83,85]. The recurrence of meningitis occurs more frequently in SCD patients [86]. The resulting pneumococcal sepsis and meningitis are common in adults, and reported cases have led to adult mortality. Treatment with a pneumococcal polysaccharide vaccine has been proposed to reduce infection, which has documented many co-morbidities, such as renal dysfunction and stroke, along with meningitis [87,88].

3.10.4. Osteomyelitis

Osteomyelitis is characterized by bone inflammation and is found in up to 61% of SCD patients, particularly in long bones such as the femur, humerus, and jaws. It is more common in SCD patients, and it is the second most affected tissue after the spleen [89]. The episodes of vaso-occlusive crisis ruptured the vasculature around the bones, allowing bacteria to infect the site, which is the primary cause of osteomyelitis [90]. Most SCD patients with osteomyelitis have Salmonella infections at multiple bone sites, which are most frequent in early childhood compared to non-SCD individuals [91,92] Furthermore, microbes such as Staphylococcus, Pneumococcus, and actinomycetes also cause osteomyelitis in SCD patients [93].

A meta-analysis shows that salmonellae are the most common bacterial pathogens of osteomyelitis in SCD in the USA and European populations. Meanwhile, *Staphylococcus aureus* is the most common pathogen in Sub-Saharan Africa and the Middle East region [94]. The predominance of Gram-negative bacteria has been linked to bowel ischemia and VOC [95]. Most of the symptoms of osteomyelitis are similar to VOC, but osteomyelitis affects fewer areas, specifically the diaphysis of a long bone [96]. As a result, physical examination, blood culture, or radiological examination are insufficient for detecting osteomyelitis in SCD, and ultrasonography or a higher imaging device for diagnosis of osteomyelitis has been suggested [97]. The clinical diagnosis of microbial osteomyelitis and bone infarction in early SCD patients is a major limitation. It has also been associated with Mycobacterium ulcers [98] and other causative agents, such as *Haemophilus influenza*, *Escherichia coli*, and *Enterobacter sps* [95]. However, early diagnosis has been suggested to prevent invasive surgical intervention and be treated through medicines/antibiotics.

3.10.5. Mycobacteria

It has been reported that iron overload is primarily known to cause organ dysfunction and also increases the risk for mycobacterial infection in SCD patients [99,100]. Shemisa et al. found that SCD Patients with iron overload were at an increased 17-fold higher risk to die from *Mycobacterium tuberculosis* in the sub-Saharan African population [101]. Thorell et al. reported that nontuberculous mycobacteria (NTM) infection, such as *Mycobacterium fortuitum*, causes frequent admissions for vaso-occlusive painful episodes in teenagers with SCD [102]. Edrees et al. subsequently confirmed an unusual *Mycobacterium avium* complex bacteremia infection in two SCD patients [103].

Another study found that the *Mycobacterium terrae* complex is a rare clinical pathogen known to cause pulmonary, bone and joint infections in a patient with febrile SCD [104]. Ashraf et al. also found *Mycobacterium mucogenicum* bloodstream infections in an outpatient setting in the USA [105]. The main risk factors of NTM in bloodstream infections are indwelling vascular catheters (IDVC), which are known to affect the immune system that causes relative immune deficiencies in SCD [106]. Recently, a Multicenter study suggests that Mycobacterium does not seem to be a risk factor for severe Tuberculosis (TB) and not a risk factor for mortality [107].

3.10.6. Urinary Tract Infection (UTI)

Urinary tract infection is a common cause of childhood morbidity and mortality in SCD. A high prevalence of UTIs with characteristics of pyelonephritis caused by Salmonella, Staphylococcus, *Escherichia coli*, and Enterobacter–Klebsiella was seen in SCD patients [108]. It was observed that scarring while healing the renal medulla and excretion of dilute urine were responsible for increased UTIs and pyelonephritis. A recent report on a longitudinal retrospective study of SCD children from Saudi Arabia showed most patients have UTIs due to bacteria and splenic dysfunction, followed by VOC. After the UTIs, compromised kidney function is a significant manifestation of SCD patients, increasing the asymptomatic bacteriuria infection in the African population [109,110].

A study revealed that homozygous HbSS has a higher rate of mortality with proteinuria than heterozygous HbAS. Furthermore, Staphylococcus species were the most

common cause of infections in SCD patients with asymptomatic bacteriuria, followed by *E. coli* [111,112]. However, the early detection and treatment of UTIs are essential in patients with SCD because UTIs can lead to impaired kidney function, scarification, and severe septicemia [113]. Acute post-infectious glomerulonephritis is another clinical manifestation observed in SCD patients [114].

3.10.7. Gastrointestinal Infections

SCD patients have frequent hypoxia–reperfusion injuries caused by VOC in the intestinal vasculature, increasing gut permeability [115]. The accumulation of microbes and their products activates neutrophils, resulting in VOC [116]. The finding of ischemic colitis as an etiology of intestinal VOC has been observed in SCD patients [117]. Researchers suggest that the intestine is the primary entry point for non-typhoidal Salmonella infection because of its increased permeability, which causes gastroenteritis [118].

Non-typhoidal Salmonella and Pneumococcus were the most prevalent causative agents known to affect children and adults in Sub-Saharan Africa with SCD [119]. The report suggested that SCD children are more likely to become infected with non-typhoidal Salmonella than non-SCD children, exaggerating the severity [120]. However, these studies indicate that changing the density of the gut microbiota could improve the intestinal health of SCD patients.

3.11. Viral Infection
3.11.1. Respiratory Infections (RI)

Lung function abnormalities, or RI, are common in children and adults with SCD and may lead to a progressive decline in lung function with age [121,122]. The respiratory system is affected by several syncytial viruses, such as influenza, rhinoviruses, human metapneumo, and para-influenza, resulting in respiratory failure, which causes ACS [123]. The symptoms and severity are similar to seasonal influenza reported in SCD children and teenagers [124]. More hospitalization rates have been observed due to seasonal influenza infection being observed more in SCD children than normal [125].

Further, children infected with the influenza virus are more prone to secondary bacterial infections, which lead to ACS [78]. The severity of asthma is one of the common comorbid factors that increase in SCD children [126]. It also observed that patients suffering from repetitive episodes of ACS could develop scattered areas of lung fibrosis, and leads to advanced chronic lung disease in SCD [127].

3.11.2. Anemia Associated with Viral Infections

Severe anemia due to a transient aplastic crisis caused by B19 parvovirus belonging to the genus Erythrovirus (family Parvoviridae) was observed in 65–80% of SCD patients. It infects the erythroid progenitor cells and obstructs erythropoiesis [128]. B19 parvovirus has been associated with ACS, splenic and hepatic sequestration, bone marrow necrosis, pain crisis, and stroke [129]. In addition, Epstein–Barr virus is also responsible for hemolytic anemia, along with splenic rupture, thrombocytopenia, agranulocytosis, hemolytic anemia, and hemophagocytic lymphohistiocytosis in patients with SCD [63].

3.11.3. Hepatitis B and C Infections

Both hepatitis B virus (HBV) and hepatitis C virus (HCV) infections have a common transmission mode and can cause chronic liver infection. The prevalence of hepatitis B infections is globally higher than hepatitis C, and the infection rate is higher in males than in females [130]. Several reports suggest that SCD children are more frequently infected with hepatitis C in African countries due to multiple transfusions [131,132]. About 10% of adults with liver dysfunction documented to be infected with hepatitis C virus [133].

Iron overload following blood transfusions is additive to the liver damage caused by HCV infection. The administration of ribavirin used to treat hepatitis C virus has been known to cause hemolysis in SCD patients, which in turn increases the complications of the

disease [134]. Some studies found that the percentage of hepatitis B was lower in vaccinated children than in unvaccinated children, indicating that vaccination can prevent hepatitis in SCD children [135,136].

3.11.4. HIV Infections

There are many crosstalks between HIV and SCD; thus, the coexistence of HIV and SCD has a synergistic effect. HIV infection was found in 0–11.5% of SCD patients [137]. HIV infection also creates a favorable environment for pneumococcal infection, which can be fatal, resulting in severe pneumonia or meningitis in SCD adults [138]. A nested case-control study by Belisário et al. showed that HIV infection increased the severity of SCD-related symptoms such as ACS/pneumonia, sepsis/bacteremia, pyelonephritis, ischemic stroke, hemorrhagic stroke, abnormal transcranial doppler, and pulmonary hypertension [139]. Furthermore, National Hospital Discharge Survey data in the period of 1997–2009 showed that SCD is associated with decreased HIV but higher HBV and HCV co-morbidities in adult African-Americans [140]. Odera et al. found that children with HIV and SCD faced significant life-threatening conditions and developed a severe hypersensitivity reaction during first-line treatment [141]. Despite various reports demonstrating the impact of HIV on the clinical outcome of individuals with SCD, the literature also shows controversial data. Studies between 1995 and 2009 by Neto et al. observed no direct link between HIV and SCD complications [142]. In addition, according to another report, SCD patients are more resistant to HIV infection, and the progression of AIDS is slower in SCD patients than in non-SCD controls [143].

3.11.5. Dengue Virus

Dengue virus is a mosquito-borne flavivirus that is most common in tropical and subtropical areas [144]. Dengue causes headaches, fever, abdominal pain, bleeding, myalgias, and loss of capillary integrity and increased mortality by up to 12.5% in SCD patients [145–147], due to their compromised immune systems, which make them more susceptible to hypovolemia and endothelial cell activation. Several reports show that the prevalence of dengue is high in geographic areas where SCD is endemic, such as the Caribbean, Central and South America, areas of Africa and the Middle East, Asia, and Oceania [63,148]. Two case studies on ten and nineteen-year-old female SCD patients with severe dengue revealed multi-organ dysfunction syndrome (MODS) and impending death [149]. A recent retrospective study found that children with the HbSC genotype had a higher rate of severe dengue and death than those with the SS genotype [150].

3.11.6. Coronavirus Disease (SARS-CoV-2)

Since 2019, SARS-CoV-2 coronavirus (COVID-19) infection has been a worldwide concern. Individuals with co-morbidities are more likely to become infected with the coronavirus. Individuals with HbSS hemoglobin have hypoxia or ACS. They are thought to be more susceptible to SARS-CoV-2 infection, which affects the lungs and respiratory tract. Case reports confirmed ACS and VOC complications in SCD patients with weakened immunity and infected with the novel coronavirus [151]. However, reports on the impact of COVID-19 in terms of severity and mortality are contradictory. Some African countries reported ACS and other co-morbidities in SCD patients with no casualties [152]. According to a survey of COVID-19 in hemoglobinopathy from the United Kingdom, the majority of patients hospitalized due to SARS-CoV-2 coronavirus infections had SCD (85.1%) and were primarily homozygous (Hb SS) patients (64.1%) [153]. Minniti et al. found that SCD patients infected with the coronavirus had a higher severity of disease (10%) and a higher risk of mortality without hydroxyurea therapy, compared to approximately 3% of the general population. The reason for the conflicting reports has been argued to be age, which could be one of the factors influencing severity and mortality, as children and young adult patients (45–50 years) have a low risk of mortality. In contrast, older SCD patients have a high risk [154]. Panepinto et al. found that SARS-CoV-2 increased the risk of severe symptoms in 69% of SCD patients [155].

However, studies in France and the United Kingdom found that patients with SCD infected with the coronavirus had a low severity and mortality rate [156,157]. Second, females died at a higher rate due to SARS-CoV-2 infections than males [158]

Researchers reported the hospitalization rate was high for SCD patients over 40 years. However, Ramachandran et al. also did not find any increased risk of severity or mortality in SCD patients with the coronavirus infection [159]. A recent study showed that SARS-CoV-2 infection increased disease severity in patients with SCD in a different population [157,160–162]. Still, the overall effect of the coronavirus needs to be elucidated through multicenter reports; the existing reports are mostly speculation rather than ground-level research. Later reports showed that remdesivir injections given with blood transfusion were an effective therapy that does not require immunosuppressive or steroid treatments [163,164].

Hydroxyurea administration may be one of the most effective ways to reduce complications such as VOC during SARS-CoV-2. The HBG2 rs7482144 (C > T) polymorphism, on the other hand, is linked to HbF levels but not to the severity of SCD [165]. The use of antimalarial drugs, specifically hydroxychloroquine, has been linked to side effects in SCD patients, such as ventricular arrhythmias and cardiac toxicity, as reported in other COVID-19 patients [166].

However, there is no evidence of the extent of the side effects or complications in SCD patients. Figure 3 depicts SARS-CoV-2 infection and the challenges of its management in SCD.
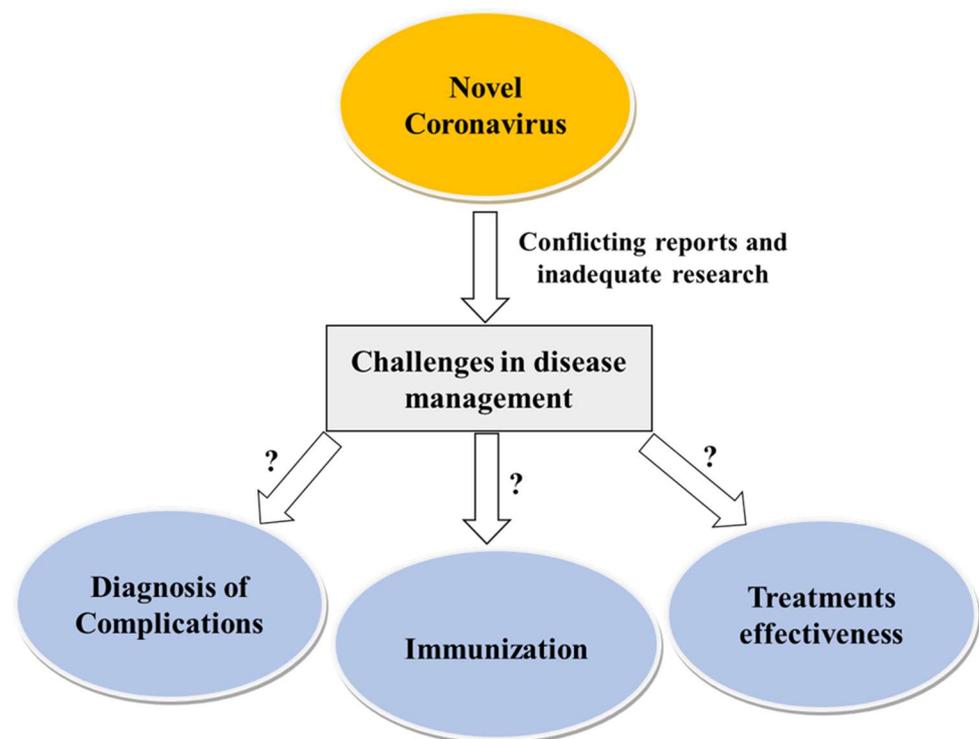

Figure 3. SARS-CoV-2 infection and challenges of its management in SCD.

3.12. Parasitic Infections

3.12.1. Malaria

Malaria is a highly vulnerable parasitic infection exhibiting fatal clinical manifestations, such as impaired splenic function in homozygous (HbSS) patients compared to HbAS or normal individuals. Individuals with HbAS show a protective effect and a lower frequency of malaria infection compared to normal individuals due to the HbAS making an unfavorable environment for malaria parasites. Moreover, the phagocytic action of infected RBC macrophages reduces infection rates [167–171]. Therefore, heterozygote individuals with the

sickle cell gene are malaria-resistant compared to normal individuals. *P. falciparum* infection is also lower due to impaired erythrocyte membrane protein 1 (PfEMP 1) binding [172].

In SCD homozygous patients, inadequate splenic functions increase the risk of *P. falciparum* infections, leading to death in children by increasing VOC [173]. However, the effect of malaria parasite infection on HbSS is fatal due to the increased severity of the already existing anemic condition and the associated pain [174]. Further severe oxidative stress is another consequence of *P. falciparum* infection in SCD patients due to increased intravascular hemolysis, ischemia–reperfusion injury, and chronic inflammation [175].

3.12.2. Other Parasitic Infections

In addition to Plasmodium, intestinal parasites such as *Entamoeba histolytica*, *Entamoeba coli*, and *Giardia lamblia*, and some helminths, such as *Ascaris lumbricoides*, *Ancylostoma duodenale*, *Trichuris trichiura*, and *Strongyloides stercoralis*, cause severe anemia in SCD patients. A study in Nigerian patients found that patients without parasitic infections had a significantly higher mean hematocrit level than patients with parasitic infections [176].

Mahdi et al. documented *Blastocystis hominis* and *Giardia lamblia* as the most common intestinal parasites in patients with SCD in Iraq and the Mediterranean [177]. Furthermore, SCD patients with schistosomiasis was found with elevated reticulocyte counts, lowered hematocrits, and augmented bacterial UTIs and their severity [178].

3.13. Treatment of Infections in SCD

Bacterial infection and sepsis are common in SCD patients as their immune systems are compromised. These should be treated with broad-spectrum antibiotics, including third-generation cephalosporins like ceftriaxone, cefotaxime oxacillin, nafcillin, or cefazolin vancomycin, and clindamycin. Penicillin, beta-lactam inhibitors, and amphotericin B deoxycholate, along with third-generation cephalosporins should be used for meningitis. For *Mycobacterium tuberculosis*, the first two months of treatment include rifampin, isoniazid, pyrazinamide, and ethambutol, followed by isoniazid and rifampin for the remaining four months. Gastrointestinal infections are caused by enteric Gram-negative pathogens, including Typhi and non-Typhi *Salmonella*, *Enterococci*, and anaerobic bacteria. These can be treated by with piperacillin–tazobactam, a carbapenem, and cholecystectomy procedures should be performed if the situation worsens. *Influenza, rhinoviruses, para-influenza, S. pneumonia, H. influenza, Chlamydophila pneumonia, Mycoplasma pneumonia*, and *S. aureus* are common pathogens that cause respiratory tract infections. The treatment options for these infections are oseltamivir, inhaled zanamivir, third-generation cephalosporins, vancomycin, clindamycin, macrolides, and quinolones. For UTIs, third-generation cephalosporins are used. Mosquitoes cause dengue and malaria, yet their causative agents are different. Nonsteroidal anti-inflammatory products, like ibuprofen and acetaminophen, are given for pain and fever with a high intake of fluids via oral or intravenous fluids. Anti-viral medicines, like chloroquine, favipiravir, and celgosivir, are continued until platelets rise to the normal range. On the other hand, intravenous quinidine is given to SCD patients infected with malaria until the parasite density is <1%.

Moreover, oral therapies are also given based on infecting parasite species. SCD patients are also very susceptible to different parasitic infections; common medicines, like albendazole, mebendazole, doxycycline, and ivermectin are given. Viral infections are very dangerous for SCD patients, as they are already suffering from other disease complications. Treatment options for viral diseases like HIV vary with antiretroviral drug resistance and adverse event profiles, and consultation with an HIV expert is recommended. The emergence of COVID-19 from SARS-CoV-2 also put SCD patients into life-threatening conditions. Hydroxyurea, L-glutamine, voxelotor, and crizanlizumab are the primary medications for preventing hemolysis and VOC. Mechanical ventilation is given if oxygen saturation decreases; supplementation with vitamins D and C and zinc also shows effective results. Convalescent plasma infusion and remdesivir with intravenous dexamethasone are given if the severity increases. Infection prevention and detailed treatment strategies are included in Table 1.

Table 1. Most common microorganisms, prophylaxis, and treatment associated with infection in sickle cell disease with underlying mechanisms for predisposition; updated from [67].

System/Infection	Mechanism	Microorganisms Involved	Clinical Manifestation	Prophylaxis	Treatment	Reference
Bacteremia/sepsis	Lack of IgG and IgM antibody response, impairments in splenic complement and opsonophagocytic functions	*S. pneumoniae, N. meningitides, H. influenza, E. coli, K. pneumonia, S. aureus,* Salmonella sp.	Septic shock with multi-organ failure	Diphtheria/tetanus/pertussis/ HIB/polio/13-valent pneumococcal vaccine; penicillin V; *Salmonella typhi* vaccine	*S. pneumonia* and other Bacteroides: third-generation cephalosporins; *S. aureus*: oxacillin, nafcillin, or cefazolin; vancomycin, clindamycin	[67–70]
Tuberculosis (Mycobacterium tuberculosis)	Cold agglutinations of anti-I specificity, hyperhaemolysis episodes	*Mycobacterium tuberculosis*	Vaso-occlusive pain episodes, hemolysis, acute chest syndrome; pulmonary dysfunction, anemia, bone and joint infections	Bacillus Calmette–Guerin (BCG) vaccine	Rifampin, isoniazid, pyrazinamide, and ethambutol for the first 2 months, and isoniazid and rifampin for the remaining 4 months	[61,103–105]
Meningitis	HLA polymorphism	*H. influenzae, H. meningitis, E. coli, S. pneumonia*	Renal dysfunction, stroke, thrombosis, silent cerebral infarction, cognitive abnormalities	Diphtheria/tetanus/pertussis/ HIB/pneumococcal vaccine/meningococcal vaccine; *S. pneumoniae* 23-valent vaccine; meningococcal vaccine; penicillin V prophylaxis	Third-generation cephalosporins; beta-lactam antibiotics; amphotericin B; intravenous acyclovir	[84,87,88]
Human immunodeficiency infection	Low CD4/CD8 ratio	HIV-1 and HIV-2	Acute chest syndrome, pneumonia, sepsis, hemorrhagic stroke, abnormal transcranial Doppler, and pulmonary hypertension	Using protection while having sex; blood should be screened for HIV before transfusion; using new and sterile needle for injection, and not using same needle for different persons	HIV expert consultation is recommended	[124]
Osteomyelitis	Abnormal opsonizing and complement function; HLA polymorphism	Staphylococcus, Pneumococcus, and actinomycetes; Typhi and non-typhi Salmonella, Gram-negative enteric bacteria, *S. aureus*	Avascular necrosis, leg ulceration (skin), osteonecrosis, bone inflammation, bowel ischemia, and vaso-occlusive crisis	Diphtheria/tetanus/pertussis/HIB; *S. pneumoniae* 23-valent vaccine; penicillin V prophylaxis	Ceftriaxone, cefotaxime; *S. aureus*: oxacillin, nafcillin, orcefazolin (MSSA); vancomycin, clindamycin	[89,93,95,179]
Urinary tract infection	Renal lesions, medullary ischemia, and perturb	Gram-negative pathogens, Staphylococcus species *E. coli*	Impaired kidney function, scarification, severe septicemia, acute post-infection	Prevention against hypoxia, acidosis, hypothermia, infection, and hypovolemia, which give rise to vaso-occlusive crisis	Third-generation cephalosporin (ceftriaxone, cefotaxime)	[111–114]
Gastrointestinal	Accumulation of microbes and their products activate neutrophils, resulting in VOC	Gram-negative bacteria, including Typhi and non-typhi Salmonella, Enterococci, and anaerobic bacteria	Common biliary duct obstruction, cholestasis, hepatic vaso-occlusive crisis, hepatic sequestration, hepatic fibrosis, and bowel infarcts	Prevention against hypoxia, acidosis, hypothermia, infection, and hypovolemia, which give rise to vaso-occlusive crisis; for gallstone formation: hydroxyurea, ursodiol, ursodoxylic acid; *Salmonella typhi* vaccine for typhoid fever	Piperacillin–tazobactam or a carbapenem; third-generation cephalosporin, piperacillin, or trimethoprim-sulfamethoxazole	[123–125]

Table 1. *Cont.*

System/Infection	Mechanism	Microorganisms Involved	Clinical Manifestation	Prophylaxis	Treatment	Reference
Respiratory tract infection	Endothelial dysfunction caused by hemolysis and release of free hemoglobin, which depletes endothelial nitric oxide, resulting in increased vasoconstriction, ischemia, and free radicals	Influenza, *S. pneumoniae*, *Mycoplasma pneumoniae*, *S. aureus*, rhinoviruses, human metapneumo, and para-influenza	Acute chest syndrome, pneumonia, chronic lung disease, pulmonary hypertension	Annual influenza vaccine; diphtheria/tetanus/pertussis/HIB/ 13-valent pneumococcal vaccine; *S. pneumoniae* 23-valent vaccine; penicillin V prophylaxis, erythromycin if penicillin allergy.	Influenza: oseltamivir, inhaled zanamivir; *S. pneumoniae*, *H. influenza* type B: third-generation cephalosporins; *S. aureus*: oxacillin, nafcillin, or cefazolin; vancomcyin, clindamycin; *Mycoplasma pneumoniae*: macrolides, quinolones	[123]
Dengue	Imbalanced and dysregulated cell-mediated immunity	Arbovirus (Flaviviridae family; genus Flavivirus)	Headaches, fever, abdominal pain, bleeding, myalgias, capillary fragility, vaso-occlusive pain, splenic sequestration, leg ulcers, heart block, plasma leakage, secondary pulmonary and brain edema, hemorrhage, and multiorgan failure	Avoid mosquito exposure by eliminating local mosquito breeding sites by eliminating standing water repositories; clogged rain gutters must be cleared; mosquito repellents: (a) wear long-sleeved clothing; (b) sleep with a mosquito net; and (c) use mosquito repellents; in Dengue-endemic areas, avoid outdoor activities during daylight hours; Dengvaxia vaccine has been approved by the FDA for children aged 9 to 45.	High fluid intake; soft diet; nonsteroidal anti-inflammatory drugs (ibuprofen); blood product transfusion (platelets); steroids, anti-viral therapy (chloroquine, balapiravir, celgosivir)	[145–147,180]
Malaria	Hypoxia, acidosis, and sickling; decreased deoxyhemoglobin solubility ultimately leads to VOC	*P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*	Vaso-occlusive pain episodes, splenic sequestration, severe anemia necessitating blood transfusions causing folate-deficiency anemia, hypoglycemia, acidosis, thrombocytopenia, and multi-organ failure	Avoid mosquito exposure; eliminate local mosquito breeding sites by eliminating standing water repositories; clogged rain gutters must be cleared; mosquito repellents: (a) wear long-sleeved clothing; (b) sleep with a mosquito net; and (c) use mosquito repellents; (d) avoid going outside at dawn and dusk.	Intravenous quinidine until the parasite density < 1% and able to tolerate oral therapy; oral therapy: based on the infecting species, possible drug resistance, and severity of disease	[172,175]

Table 1. *Cont.*

System/Infection	Mechanism	Microorganisms Involved	Clinical Manifestation	Prophylaxis	Treatment	Reference
Parasitic infections	Stimulation of the growth of antibody-producing B cells rather than stimulation of the proliferation of specific antiparasite B-cells; proliferation of suppressor T-cells and macrophages, which inhibit the immune system by excretion of regulatory cytokines; production by the parasite of specific immune-suppressor substances; damages host tissues, causing the release of stimuli that activate various cells, including innate immune cells such as macrophages, dendritic cells, eosinophils, basophils, and mast cells	Protozoa (other than malaria): *E. histolytica, E. coli* and *G. lamblia* Helminths: *Ascaris lumbricoides, Ancylostoma duodenale, Trichuris trichiura, Strongyloides stercoralis* Schistosomiasis (*S. mansoni, S. haematobium, S. japonicum*), Toxocara canis, filariasis (*Onchocerca volvulus*)	Chronic Giardia infection with secondary chronic intestinal malabsorption and failure to thrive; toxic megacolon, fulminant colitis, ulcerations on the colonic mucosa, secondary perforation; hepatic, pleural, lung, and pericardium abscesses (*E. histolytica*); vaso-occlusive pain episodes, chronic iron deficiency, and chronic eosinophilia; malnutrition, delayed growth, and cognitive deficit; acute intestinal obstruction accompanied by peritonitis and intestinal perforation; appendicitis; common bile duct obstruction accompanied by secondary biliary colic, cholangitis, or pancreatitis; hepatosplenomegaly, bloody diarrhea, portal hypertension, ascites, esophageal varices, and hematemesis are all symptoms of hepatosplenomegaly; visual impairment/blindness (filariasis, *T. canis*)	-*E. histolytica*: (a) Asymptomatic cyst excretion: paromomycin or diiodohydroxyquino-line/iodoquinol; (b) invasive colitis or extraintestinal disease: metronidazole or tinidazole, followed by diiodohydrox-yquinoline/iodoquinol or paromomycin; (c) percutaneous or surgical aspiration of large liver abscesses; (d) piperacillin–tazobactam or meropenem if peritonitis; -Giardiasis: metronidazole, nitazoxanide, or tinidazole; hand hygiene after defecation; sanitary disposal of fecal material; treatment of drinking water (boiling, chemical disinfection with iodine or chlorine, use of filters); avoid using recreational water venues (e.g., swimming pools, water parks) until asymptomatic and treatment is complete; chemotherapy prophylaxis: albendazole, mebendazole; community-wide mass ivermectin treatment	Albendazole, mebendazole, pyrantel pamoate, ivermectin, doxycycline albendazole, mebendazole, pyrantel pamoate, ivermectin, doxycycline	[176–178,181,182]
COVID-19	Progressive endothelial activation with the risk of micro- and macrothrombi, and disseminated intravascular coagulation (DIC)	SARS-CoV-2	Acute chest syndrome, severe pneumonia, hemolysis, vaso-occlusive pain episodes, stroke, reduced oxygen saturation, fever, headache, sore throat, mild to severe cough, weakness, fatigue, difficulty breathing	Frequent hand sanitization; avoid touching face; wear mask; maintain at least 1 m distance from other persons to avoid infection	Hydroxyurea, L-glutamine, voxelotor, and crizanlizumab with vitamins D, C, and zinc; azithromycin; ivermectin; tocilizumab dexamethasone; convalescent plasma infusion; remdesivir with intravenous dexamethasone	[153,163,164,183]

4. Future Perspective and Roadmap for Research and Implementation

In a nutshell, a roadmap for SCD research can be developed to diagnose symptoms and design effective therapies to reduce complications in sickling patients. The goal of treatment is to reduce the complications of symptoms that lead to hospitalization, suffering, and early death, particularly in children. Research is being conducted to target various pathways and mechanisms that lead to SCD complexity extensively. Rapid test kits for SCD, such as the rapid Sickle SCAN® point-of-care (POC) test, are a less expensive, more affordable, and more accurate early mode of diagnosis in economically underdeveloped areas, where previously available SCD diagnostic methods required a well-equipped laboratory and were time-consuming. Therefore, high-accuracy kits could be promoted in low-income countries with endemic SCD.

A technology- and algorithm-based cost-effective screening of SCD (smartphone-based microscope and deep-learning) has been proposed; similarly, research on the diagnosis of infections could be a better non-invasive strategy. Physical examination and blood culture determination of the extent of infections are insufficient, and the invasive methods are painful. As a result, researchers advocate for using advanced non-invasive techniques, such as ultrasonography and imaging techniques, to thoroughly diagnose the severity of the infection and its clinical manifestation when the first symptoms of infection appear and to plan appropriate treatment. Treatments with antibiotics to suppress the infection are not sufficient for patients with high risk.

Consequently, many therapeutic strategies targeting the various pathways leading to complications in SCD are currently in use. At the molecular level, medication based on antibiotics or antibodies has proven to be a better therapeutic approach that reduces mortality while decreasing pain in SCD patients. Antibiotics such as voxelotor have recently been shown to prevent hemoglobin polymerization in SCD patients. Its concentration rises in the blood, allowing oxygen to circulate throughout the body aiding. Oral administration of pharmaceutical-grade l-glutamine has also been reported to reduce oxidative stress, and thus, pain, with minimal or no toxic effect on patients, as has the administration of the anti-P-selectin (P-selectin binds on endothelial cells and platelets) monoclonal antibody crizanlizumab to reduce and delay the first vaso-occlusion crisis and the resulting pain. Gene therapy or hematopoietic stem cell transplantation to form fetal hemoglobin to restore normal hemoglobin in SCD patients could be one method of implementing a systematic approach. The screening and resistance to antibiotics of new variants or mutant genetic strains, such as the self-mutable highly pandemic coronavirus severe acute respiratory syndrome coronavirus 2 on SCD patients, are currently some of the significant challenges. As mutant variants have different degrees of resistance to antibiotics, the effect of immunization against the coronavirus on SCD patients of varying age groups with existing co-morbidities must be monitored carefully and meticulously. Research on many aspects, such as incubation time and recovery period during viral or any other microbial infections, are of great concern. Thus, research on molecular, antigen, serological, and internal physical testing to determine the extent of the complications on different biological systems, the effectiveness of immunization, and therapy is a priority.

5. Conclusions

Pneumonia, meningitis, osteomyelitis, and UTIs are prevalent among individuals with SCD in developing countries, constituting the leading factors behind its morbidity and mortality. It has also been observed that the primary infectious symptoms occur in children under the age of five, necessitating the need for immediate treatment. Priorities for the future management of infectious complications in SCD vary according to geography and socioeconomic status. Susceptibility to infection varies among individuals and across age groups. Some patients have chronic hemolytic anemia with vital organ failure due to infarctive damage, while others have no or few medical problems. A better understanding of the mechanisms underlying the increased susceptibility of these patients to infection may

lead to interventions that address the underlying cause in the future. Meanwhile, the early detection and treatment of infections with hydroxyurea and blood transfusions can help to avoid severe complications and splenic dysfunction. Simultaneously, primary interventions, such as penicillin prophylaxis and vaccinations, result in significant improvements in SCD patients.

Nonetheless, these therapies are associated with substantial risks, making their routine use inappropriate. However, if a more precise and comprehensive analysis of the genetic variations conferring an increased risk of infection and testing could help stratify patients into high-risk groups, the frequency of crises could be reduced by improving the QOL of SCD patients. Additionally, it could help to postpone long-term challenges, thus also enhancing life expectancy.

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