REVIEW ARTICLE

Infections in sickle cell disease

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Abstract

Sickle cell disease (SCD) is one of the commonest severe inherited disorders in the world. Infection accounts for a significant amount of the morbidity and mortality, particularly in sub-Saharan Africa, but is relatively poorly studied and characterized. Patients with SCD have significant immunodeficiency and are more likely to suffer severe and life-threatening complications of infection, and additionally infections can trigger complications of SCD itself. Those with more severe forms of SCD have functional asplenia from a very early age, which accounts for much of the morbidity in young children, particularly invasive infections from encapsulated bacteria including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Salmonella typhi* and meningococcal disease. Additionally, there are other defects in immune function in SCD, associated with anemia, tissue infarction and impaired adaptive immunity. Complications of infections in SCD include acute chest syndrome, acute painful episodes, osteomyelitis, meningitis, urinary tract infections, overwhelming sepsis and death. Viral infections cause significant morbidity, particularly severe anemia associated with parvovirus, and to a lesser extent other infections such as influenza and coronavirus disease 2019. The relationship between malaria and SCD is complicated and discussed in this review. Unlike many of the genetic risk factors for poor outcomes in SCD, it is theoretically possible to modify the risks associated with infections with established public health measures. These include the provision of vaccination, prophylactic antibiotics and access to clean water and mosquito avoidance, although current financial restraints and political priorities have made this difficult.

Immune function in sickle cell disease

Sickle cell disease (SCD) causes severe acute complications and chronic illness, driven by vaso-occlusion and hemolytic anemia.[1] A significant part of the high morbidity and mortality in SCD is associated with an increased risk of infection – bacterial, viral and parasitic (Figure 1). This is in part due to progressive organ damage caused by recurrent vaso-occlusion, most notably splenic injury.[2]

Hyposplenism

Invasive bacterial infections are a common occurrence in both children and adults with SCD. This is in large part due to the impairment of splenic function that develops in early childhood, leaving children with SCD extremely vulnerable to infections with encapsulated bacteria, such as *Streptococcus pneumoniae*.[3] The exact pathophysiology of hyposplenia in SCD remains unknown, but it is thought to be a consequence of repeated intrasplenic sickling causing infarction and inflammation, ultimately leading to progressive splenic fibrosis and, in some cases, complete splenic atrophy (autosplenectomy).[4] In children with HbSS, hyposplenism typically develops within the first year of life.[5,6] The onset of splenic dysfunction in subjects with other sickle cell genotypes is yet to be examined in detail, but as a precaution these children are most often presumed to be asplenic from an early age.

Other aspects of immune dysfunction

A full review of immune function in SCD is beyond the scope of this review but, briefly, in addition to hyposplenism, immune function is abnormal in several other ways. SCD is associated with chronic inflammation, driven by infection,

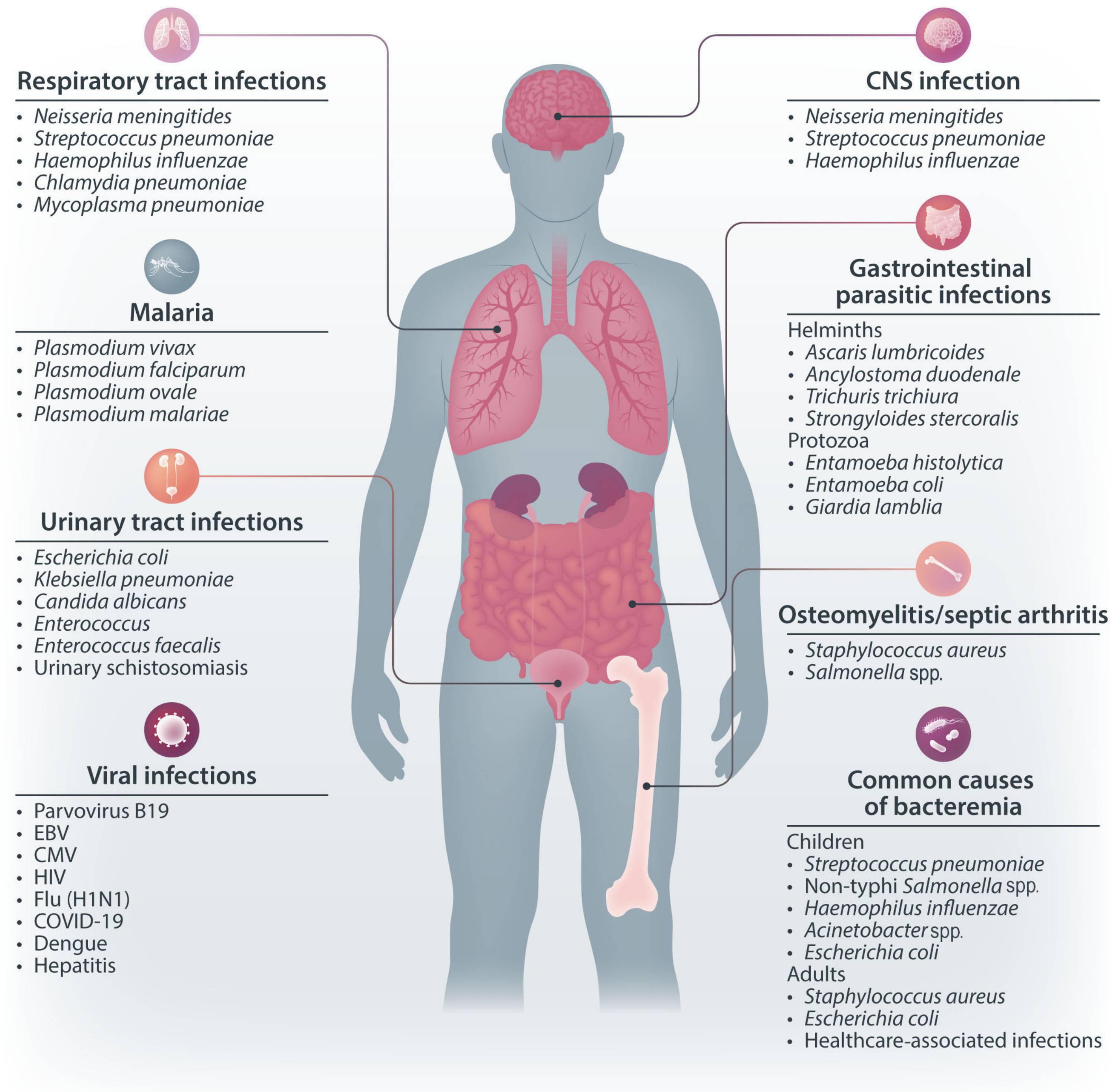

Figure 1. Diagrammatic overview of key infections in sickle cell disease by organ system. EBV: Epstein-Barr virus; CMV: cytomegalovirus; HIV: human immunodeficiency virus; Flu: influenza; COVID-19: coronavirus disease 2019.

infarction and hemolysis, which leads to an overactive and dysregulated immune system, as shown by an increased incidence of autoimmune diseases, and evidence of uncontrolled macrophage activation causing various complications, such as severe hemolytic transfusion reactions.

There is also evidence of immunodeficiency, with abnormalities of both the innate and adaptive immune systems. In addition to hyposplenism, innate immunity is impaired by tissue infarction allowing increased entry of bacteria through the skin, as occurs with leg ulcers, and the gastrointestinal tract; areas of infarcted tissue within the body, particularly in bones, further act as foci of infection.[7]

There are also less well documented deficiencies of adaptive immunity, with abnormalities of both B- and T-cell subsets and function.[8] For example, studies suggest that children with SCD make relatively poor antibody responses to vaccination against pneumococcus and influenza, with lower and less persistent levels of antibodies, although importantly these vaccinations still seem to offer significant protection against infection. The complement pathway is also abnormal, with reduced opsonization of bacteria.

Some treatments used in SCD also add to the immunodeficiency. Blood transfusions have been shown to increase the risk of infection, and the accompanying iron overload also predisposes towards certain infections, particularly Yersinia, but possibly also tuberculosis and malaria. Increasing numbers of patients have been treated with stem cell therapies which require exposure to myeloablative chemotherapy and long-term immunosuppression, with the accompanying increased risk from many pathogens. Importantly, although hydroxycarbamide does cause myelosuppression, it does not cause significant immunosuppression in SCD, and indeed reduces the risk of many infections, probably by offering better control of the SCD itself.[7]

Without appropriate treatment and prophylaxis, infections in SCD can be life-threatening, particularly for young children. Furthermore, infections are associated with exacerbation of other sickle-complications, often precipitating vaso-occlusion and pain as well as acute severe hemolysis. Since the introduction of antimicrobial prophylaxis and immunizations, most children born with SCD in Europe and North America survive to adulthood.[9-11] Sadly, this is not the case in many low-income countries, where a lack of neonatal screening and early diagnosis remains an obstacle to initiation of even simple prophylactic measures, such as daily penicillin.

As is true for most research in SCD, most studies on infections in SCD examine complications and outcomes in individuals with homozygous HbSS, sickle cell anemia (SCA). As such, the main focus of this review is clinical infections in individuals with SCA.

Bacterial infections in sickle cell disease

It was established in the 1960s that children with SCA are particularly susceptible to infections with *S. pneumoniae*, with septicemia, meningitis and pneumonia caused by this organism being major causes of early childhood mortality.[12] Twenty years later, the Cooperative Study of Sickle Cell Disease found that the annual incidence of pneumococcal sepsis in SCD was 10 cases per 100 person-years, observed in 335 children under the age of 3 years.[13] The case-fatality rate was 30%. This observation led to the initiation of the pivotal PROPS (Prophylaxis with Oral Penicillin in Children with Sickle Cell Anemia) study, which greatly reducing morbidity and mortality in children with SCD.[14] Today, antibiotic prophylaxis remains a cornerstone of treatment in under 5-year olds with SCA, although there is a need for more evidence on its use in older patients and different types of SCD.

The pharmacokinetics of many antibiotics are likely to differ significantly in people with SCD compared to the non-sickle population. This is probably mainly related to differences in renal function, which change with age; children develop glomerular hyperfiltration at a young age, which gradually falls throughout life, such that the majority of older adults have some degree of renal impairment. Other factors which may alter the pharmacokinetics of antibiotics include varying degrees of hepatopathy, chronic inflammation and the co-administration of other drugs, such as hydroxycarbamide. There are few studies which have looked at this specifically, although one found that the clearance of ciprofloxacin was greater in children with SCD and suggested that dosing should be changed accordingly.[15] In general, it is appropriate to monitor antibiotic levels where possible in patients with SCD, particularly when treating severe infections or when patients are not responding to treatment as expected.

Respiratory infections

Respiratory infections are common in individuals with SCD and can be associated with serious complications such as vaso-occlusion and acute pain, as well as acute chest syndrome (ACS). Furthermore, there is a high risk of respiratory infections with encapsulated bacteria progressing into septicemia if appropriate antibiotic treatment is not rapidly commenced, especially in young children.

ACS is defined as an acute illness with respiratory symptoms with or without fever and new pulmonary infiltrates on plain chest X-ray. It is a major cause of critical illness and the third most common cause of death in adults with SCD in the UK.[16] The etiology of ACS is multifactorial and remains ill defined; a cause is confirmed in less than half of patients, but many cases are caused by bacterial infections.[17] Current UK ACS guidelines suggest parenteral antibiotic treatment with cover for atypical organisms as part of the mainstay of ACS treatment, even if cultures are negative.[18] Antibiotic choice should be guided by local policies. Recommended microbiology investigations in a patient with ACS include serology for atypical organisms and urine sampling for legionella and pneumococcal antigens, although the sensitivity and specificity of the latter is limited, particularly in children. As transmission of these pathogens is mostly via respiratory droplets it is important that appropriate infection prevention and control precautions are taken. In this section we discuss key bacteria responsible for respiratory infections in SCD.

Streptococcus pneumoniae

S. pneumoniae, often referred to as pneumococcus, is a facultative anaerobe, Gram-positive bacterium. *S. pneumoniae* is a commensal organism of the upper respiratory tract in healthy individuals, causing community-acquired pneumonia when it migrates to the lungs.[19] Pneumococcal infection is a predominant cause of mortality among children with SCD, due to its relative abundance and frequency of progression to septicemia (children <5 years with SCD are at a 400-fold increased risk[20]). Its associated clinical syndromes includes lower respiratory tract infection, ACS, meningitis and overwhelming sepsis; preceding or concomitant viral infection is a common feature.[21]

Hyposplenism predisposes to severe pneumococcal infection in SCD. However, animal studies have shown that healthy mice with functioning spleens, transplanted with sickle cell bone marrow, still suffer from more severe pneumococcal infection compared to non-sickle mice,[22] the proposed mechanism of susceptibility being upregulated platelet-activating factor receptor. Before preventative measures were introduced, children with SCD were 30-600 times more likely to develop invasive pneumococcal disease than children without SCD.[23] These numbers have significantly improved with the introduction of effective penicillin prophylaxis and the pneumococcal conjugate vaccine. The rates of invasive pneumococcal disease have decreased by as much as 93.4% in children <5 years old, and an associated decrease in ACS has been observed in French studies since vaccine introduction.[23,24] Nonetheless, antimicrobial treatment is becoming more challenging with evolving β-lactam resistance.[19] Rates of early childhood mortality in SCD remain high in most low-income settings and it has been estimated that 50-90% of children living in sub-Saharan Africa continue to die before their 5th birthday, most as a consequence of invasive bacterial infections.[25-27] Early case series suggested that more than 40% of cases of ACS were caused by *S. pneumoniae* infections,[3] although it has become increasingly uncommon. In most studies over the last 20 years, pneumococcal infection accounts for fewer than 5% cases, reflecting widespread use of penicillin prophylaxis and effective vaccinations.[28]

Haemophilus influenzae

Another encapsulated bacterium that poses a respiratory threat in SCD is *Haemophilus influenzae*. Before the introduction of effective vaccination in 1992,[29] mortality from invasive *H. influenzae* type B (Hib) in children with SCD was very high at 20-30%.[30,31] Hib infection often presents with low grade fever, otitis media and symptoms of upper respiratory tract infection, but can progress to meningitis or septicemia resulting in multi-organ failure.[20]

In a post-vaccine and antimicrobial prophylaxis era, Hib infections have decreased, although they have not been eradicated. A retrospective single-center study from the United States (US) identified an incidence of 0.58/1,000 person-years for children with SCD aged 0 to 18 years old, but no deaths.[31] In contrast, another US center identified no Hib bloodstream infections in SCD over a 10-year study period.[32] This observed improvement in Hib infections in SCD may not be a global effect. A study from Kenya showed a Hib bacteremia incidence of 12% between 1998-2008.[33] This, however, is likely to be an underestimate as more than 90% of children with SCD in sub-Saharan Africa die before the diagnosis is confirmed.[33] Improved access to vaccines in these low- and middle-income countries is key, although more studies are needed on response to the Hib conjugate vaccine in SCD.[34]

Chlamydia pneumoniae

Chlamydia pneumoniae is an obligate intracellular bacterium that has a propensity to infect endothelial cells and has been shown to induce inflammatory responses, which are commonly observed in atherosclerosis.[35] It has been implicated in the pathogenesis of ACS, with polymerase chain reaction positivity for *C. pneumoniae* found in 13-14% of cases.[36,37] A positive polymerase chain reaction in ACS was associated with older age, lower hemoglobin concentration and chest pain. Despite its proposed association with endothelial inflammation, Goyal *et al.*[38] demonstrated that *C. pneumoniae* infection was not associated with an increased risk of stroke in a pediatric SCD population. There is no effective vaccine and strains of *C. pneumoniae* are showing increasing resistance to β-lactams,[39] making treatment increasingly difficult.

Mycoplasma spp.

Mycoplasma pneumoniae is a small bacterium, lacking a cell wall, which is a common respiratory pathogen in all populations, accounting for 10-40% of all cases of community-acquired pneumonia.[40] In SCD, a serological diagnosis of mycoplasma infection is found in approximately 9% of all cases of ACS, and 12% of ACS cases occurring in children under 5 years old.[41] Case reports suggest that mycoplasma may cause a particularly severe form of ACS, with prolonged fever lasting more than 7 days, pleuritic pain and pleural effusions.[42] *M. pneumoniae* accounts for most mycoplasma infections in ACS, although *M. hominis* and *M. tuberculosis* also occur.[41] Mycoplasma infections do not respond to penicillin-based antibiotics and treatment with a macrolide is necessary.

Treatment of respiratory bacterial infections in sickle cell disease

Respiratory bacterial infections are a serious threat to patients with SCD, both because of their reduced immunity and because of the potential of respiratory complications to cause hypoxia and exacerbate hemolysis and vaso-occlusion, with rapid clinical deterioration. Treatment and investigation require multidisciplinary management, including the involvement of microbiology, critical care and respiratory medicine colleagues. The management of ACS includes the routine use of parenteral antibiotics, typically including a broad-spectrum penicillin or cephalosporin, with a macrolide to cover atypical organisms.

Routine immunization remains one of the most effective defense strategies against respiratory bacterial infections in SCD, as part of the childhood immunization schedule (Table 1).[43,44] Vaccine uptake however, has been reported to vary widely geographically (46-95%)[45-47] and further work is needed to ascertain response to vaccines in SCD. Hydroxycarbamide therapy has been shown to reduce episodes of ACS and infective complications in SCD and to inhibit progression of pneumococcal disease in a murine model.[48] Penicillin prophylaxis (or erythromycin in patients allergic to penicillin) protects against pneumococcal infection,[49] although the duration of prophylaxis varies between countries. The impact of education and infection prevention and control measures are likely to be important, particularly in low-resource settings.

Osteomyelitis

Osteomyelitis is a characteristic infective complication of SCD, with the potential for chronic infection and long-term

Table 1. Recommended immunizations in sickle cell disease in the United Kingdom, assuming the patient has been diagnosed with sickle cell death from birth, up to date at the time of writing. Adapted from NICE (2021)[43] and UK Health Security Agency (2023).[44]

Scheduled administration	Immunizations
8 weeks	Diphtheria, tetanus, pertussis (whooping cough), polio, *H. influenzae* type b and hepatitis B Meningococcal group B Rotavirus gastroenteritis
12 weeks	Diphtheria, tetanus, pertussis, polio, *H. influenzae* type b and hepatitis B Pneumococcal conjugate vaccine Rotavirus
16 weeks	Diphtheria, tetanus, pertussis, polio, *H. influenzae* type b and hepatitis B Meningococcal group B
From 6 months	Seasonal influenza vaccine (annually thereafter)
Within the first year of life	Meningitis ACWY vaccine (two doses at least 4 weeks apart during first year of life)
1 year	*H. influenzae* type b and meningococcal group C Pneumococcal conjugate vaccine booster Measles, mumps and rubella Meningococcal group B booster
8 weeks after 1-year vaccinations	Meningitis ACWY booster
2 years	Pneumococcal polysaccharide vaccine (PPV23) and every 5 years thereafter
3 years and 4 months	Diphtheria, tetanus, pertussis and polio Measles, mumps and rubella booster
12-13 years	Human papilloma virus vaccine
14 years	Tetanus, diphtheria and polio Meningitis ACWY
Schedule undefined	Vaccination against novel infectious pathogens as advised by public health authority e.g., SARS-CoV-2 Travel vaccinations as per current advice for the destination of travel

morbidity. Subjects with SCD are at an increased risk of bone infection due to hyposplenism and ischemic damage to bone, with the most common location of osteomyelitis being at the site of bone infarction.[50] In SCD the bone marrow is expanded due to increased hematopoiesis and acts as a reservoir for bacterial expansion. It is difficult to distinguish between osteomyelitis and vaso-occlusion clinically, as both present with painful swollen bones, although vaso-occlusion is many times more common. A case-control study suggested that those presenting with bony pain and swelling affecting a single site and prolonged fever are more likely to have osteomyelitis,[51] although the definitive diagnosis relies on microbiological evidence of infection, with the culture of an organism from blood, bone or subperiosteal fluid. The true incidence of osteomyelitis in SCD is not known, but in a French study of 299 people with SCD over a period of about 4 years, 12% developed osteomyelitis. Two organisms account for most of the infections.[52]

Staphylococcus aureus

Staphylococcus aureus is a Gram-positive, non-capsulated bacillus, a skin commensal and the most common cause of osteomyelitis in the UK general population, and the most common cause of osteomyelitis in SCD in sub-Saharan Africa and the Middle East.[53,54] In a European study, *S. aureus* was the second most common organism cultured from patients with osteomyelitis with SCD, after *Salmonella* spp., accounting for 18% cases.[55] Bone is a dynamic organ, especially in SCD with increased marrow turnover, and it serves as an attractive target for bacteria. *S. aureus* spp. possess microbial surface components recognizing adhesive matrix molecules which aid their invasion of bone and pathogenesis in osteomyelitis.[56] Increasing challenges in treating *S. aureus* are mainly due to resistance including methicillin-resistant species. Mechanisms of treatment failure are polyfactorial, resulting from bacterial and host factors, but prompt initiation and escalation of treatment is vital in these cases.[57]

Salmonella spp.

Salmonella spp. are Gram-negative bacilli, of which *S. typhi* is the only encapsulated organism.[58] In the post-pneumococcal vaccine era, non-typhoidal *Salmonella* spp. were the leading cause of invasive bacterial infection in a European pediatric SCD population.[55] Salmonella bacteremia was associated with a 77% incidence of osteomyelitis in SCD.[59] Salmonella infections are more prevalent in US and European regions, but some controversy exists and further updated work is needed to confirm this.[53,54,60] Proposed mechanisms for increased vulnerability to Salmonella infections in this group include increased intestinal permeability due to hypoxic injury during vaso-occlusion and alterations in gut microbiota contributing to increased risk of gut translocation.[61] Unconjugated and live attenuated Salmonella vaccines exist but are not routinely recommended in SCD; a recent Cochrane review identified a need for clinical trials in this area.[62]

Other bacterial infections causing osteomyelitis

Case reports and series have identified a range of other bacteria causing osteomyelitis in SCD, particularly Gram-negative enteric bacilli, including *Escherichia coli*,[63] *Klebsiella*,[63] *Bacteroides fragilis*,[64] *Enterobacter cloacae*[65] and *Pseudomonas aeruginosa*,[65] which possibly enter the blood and cause bone infection via intestinal infarction. Mycobacterial infection has been identified as a cause of osteomyelitis, both as a result of pulmonary tuberculosis[67] and a Buruli skin ulcer caused by *Mycobacterium ulcerans*.[67]

Treatment of osteomyelitis in sickle cell disease

Management of osteomyelitis in SCD needs to be multidisciplinary with appropriate involvement of microbiology and surgical colleagues. In definite cases of osteomyelitis, with typical radiological appearance and microbiological proof of infection, treatment typically involves a prolonged course of antibiotics. Source control in the form of surgical debridement, especially if there is a prosthesis present, is an important part of management, although surgery is not necessary in the majority of cases.[68] Current consensus is that targeted intravenous antibiotic therapy for 4-6 weeks is important for good outcomes.[50] A Cochrane review in 2019[69] revealed no existing clinical trials assessing the efficacy and safety of antimicrobial approaches to osteomyelitis treatment in SCD and there is a need for further research. Osteomyelitis of the facial bones is not uncommon in SCD due to the nature of the vasculature in this area and in these cases close collaboration with maxillofacial or dental colleagues is needed.[70]

Other infectious syndromes in sickle cell disease

Meningitis

Neisseria meningitidis is another encapsulated organism with increased virulence in SCD due to hyposplenism. It is the causative organism of a group of infectious illnesses collectively known as meningococcal disease. *N. meningitidis* is transmitted via respiratory droplets and replicates in the nasopharynx of hosts before entering the bloodstream.[71] However, it has not been commonly implicated in the pathogenesis of respiratory infections in SCD or as an infectious agent in ACS.[17] It causes bacterial meningitis, entering the central nervous system via the ethmoid bone or the bloodstream and has an overall mortality of 13% in the general population.[71] In a study from a US national database of 533 SCD admissions from 2016-2019, none had culture-positive *N. meningitidis*.[72] This is perhaps due to the efficacy of vaccinations or early initiation of treatment resulting in poor culture yield. The exact prevalence of meningococcal infection in SCD is poorly studied. It is unclear why splenic dysfunction in SCD causes a greater risk of pneumococcal disease than meningococcal disease.[50] Penicillin resistance is an issue with *N. meningitidis* and third-generation cephalosporins tend to be the treatment of choice.[73]

Urinary tract infections

Urinary tract infections are thought to be relatively common in SCD, due to hyposplenism, renal ischemia and infarction, and impaired urinary concentration and acidification, although there are relatively few studies. A US study found that 4.1% children under the age of 4 years with SCD who were febrile had evidence of a urinary tract infection, with *Escherichia coli* accounting for most of the cases, which is similar to the incidence in the non-SCD population.[74] Studies from sub-Saharan Africa generally suggest higher rates of urinary infections in SCD; for example, a study from Tanzania found that about 29% of girls and 14% of boys had a urinary tract infection based on dipstick testing, with *E. coli* being the most commonly isolated organism, and *Klebsiella*, *Staphylococcus*, *Proteus* and *Pseudomonas* spp. also identified.[75] Similarly a cross-sectional study from Zambia found that 25% patients with SCD had bacteriuria.[76] Based on these limited data, febrile patients with SCD should be tested for possible urinary tract infections and, if present, these should be investigated and treated in the usual way.

Bacterial prophylaxis in sickle cell disease

The use of antimicrobial prophylaxis against invasive bacterial infections in SCD is recommended in most guidelines, although the evidence for this largely comes from studies before anti-pneumococcal vaccines were in use, and there is little consensus on how long antimicrobials should be continued. A randomized, double-blind, placebo-controlled trial of penicillin in children with SCA under the age of 3 years (PROPS) was published in 1986 and showed an 84% reduction in infections in the penicillin arm; three deaths occurred due to pneumococcal septicemia, and all of these were in the placebo arm.[14] The subsequent PROPSII study, published in 1995, suggested that it was safe to discontinue penicillin prophylaxis after the age of 5 years in children who had received the 23-valent pneumococcal vaccine, but the study was not sufficiently powered to detect meaningful differences between the two arms.[77,78] There is no evidence of harm from long-term penicillin, although drawbacks include its contribution to antimicrobial resistance, potential side effects, and issues with long-term adherence. All available guidelines recommend the use of prophylactic penicillin, or erythromycin if there is penicillin allergy, in children with SCA (HbSS and HbS/β^0 thalassemia), but there is less certainty about how long it should be continued. For example, in the US most guidelines suggest it can be stopped at the age of 5 years,[79] whereas in the UK lifelong penicillin is recommended. In other countries, such as France, penicillin is typically stopped when children start secondary school at around the age of 10 years, and in many sub-Saharan countries its use is largely determined by availability and affordability, meaning that many patients do not get it.[80] Adherence to treatment with penicillin is variable and an important determinant of its effectiveness. Various studies suggest that adherence varies between about 40% and 80%, and there is anecdotal evidence that a significant proportion of deaths in children with SCA in some countries could have been prevented by the effective use of penicillin.[80] It is likely that explaining to patients and families about why penicillin is necessary increases adherence significantly. Further studies are needed to look at the effectiveness of penicillin prophylaxis, particularly considering the increasing importance of penicillin resistance.

Vaccination (Table 1) and treatment of the underlying SCD remain effective strategies for preventing infection. A study of Ugandan children showed that initiating hydroxycarbamide reduced infections by 60% (P<0.001),[81] and data from the REACH trial showed a reduction in both malarial and non-malarial infections[82] with hydroxycarbamide. There is a lack of evidence whether anemia confers a vulnerability to infection, and transfusions still carry a risk of infection in many countries.[83] Immunosuppression for hematopoietic stem cell transplantation and gene therapy in SCD increases vulnerability to infections, and in the immediate post-transplant period infections can be life-threatening. As new SCD therapies emerge, monitoring their effect on infections is an important safety outcome.

Viral infections

Viral pathogens cause significant morbidity and mortality in those with SCD. Complications range from mild to life-threatening and can predispose to secondary bacterial infection. The overall burden of morbidity and mortality of viral infections in SCD is largely unknown.

Parvovirus B19

Human parvovirus B19 is a linear single-strand DNA virus transmitted via respiratory droplets.[84] It is the causative pathogen of erythema infectiosum (fifth disease) and slapped cheek syndrome and has an affinity for erythroid progenitor cells, using surface p-antigen as a receptor. This causes a temporary pause in erythropoiesis and transient red cell aplasia. In SCD, this presents with fever and pain, with a rapid fall in reticulocytes and life-threatening anemia, typically lasting 7-10 days.[85] Treatment centers around transfusion and supportive care to prevent circulatory collapse, alongside the management of complications, including ACS, increased splenomegaly, nephropathy, fat embolization/bone marrow necrosis and cerebrovascular complications, possibly in association with increased anemia.[86,87] Infection typically resolves spontaneously resulting in long-term immunity, although in about 3% of patients, viremia may persist and cause prolonged anemia. Hydroxycarbamide does not seem to be associated with an increased risk of persistent parvovirus infection.[88]

The seroprevalence of parvovirus in studies varies widely based on geographical location, socio-economic status, age at serological testing and transfusion history.[85] A US study in children found that the incidence was 11.3 cases per 100 patient-years.[87] No commercially available vaccine currently exists.

Human immunodeficiency virus

Human immunodeficiency virus (HIV) has a prevalence of up to 11.5% in some SCD populations, compared to 0.7% worldwide.[89,90] This is largely explained by the geographical overlap in sub-Saharan countries where the prevalence of both conditions is high and access to care for both is limited.[89] Little is understood about the significance or mechanisms of co-existence, and there is a lack of clinical guidelines on how to manage this unique group of patients. SCD has been suggested to reduce the progression of HIV to acquired immunodeficiency syndrome.[89] Many mechanisms have been proposed but none definitively proven, including HIV resistance-conferring allelic variants, altered immunity in SCD, and the absence of a functional spleen, which is a site of HIV invasion and replication in healthy controls. Clinical and *in-vitro* studies have also implicated hydroxycarbamide as virostatic in HIV infection.[91] Both conditions independently increase risk of stroke, avascular necrosis, pulmonary hypertension and co-existence increases risk of HIV and SCD complications.[89] Some case reports suggest that antiretroviral therapy may induce acute painful episodes in SCD, but it is unclear whether these medications cause this directly or indirectly via cytokines.[92]

Influenza

Influenza is a respiratory viral infection associated with excess morbidity and mortality in SCD. It is distributed in a seasonal pattern and can cause epidemics. Children with SCD are 56 times more likely than healthy counterparts to be hospitalized with influenza although there does not seem to be an increased risk of admission to intensive care or death.[93] ACS guidelines[18] recommend routine nasopharyngeal aspirate for influenza A (including the H1N1 subtype) and influenza B as part of routine diagnostic workup, and suggest antiviral agents should be used if there is clinical suspicion of H1N1 infection in ACS (severe subtype of influenza A). Influenza confers an increased susceptibility to secondary bacterial lower respiratory tract infections.[58] It is generally recommended that people with SCD receive annual vaccination against influenza where this is available, although more evidence is needed regarding the efficacy of this in SCD.[94,95]

Coronavirus disease 2019

Underlying cardiopulmonary comorbidities and immunocompromise make those with SCD vulnerable to respiratory severe acquired respiratory coronavirus 2 (SARS-CoV-2) infection. In a systematic review and meta-analysis,[96] it was shown that when adjusted for confounders, SCD patients were more likely to die (odds ratio=1.86; 95% confidence interval: 1.30-2.66) and be hospitalized (odds ratio=5.44; 95% confidence interval: 1.55-19.13) with coronavirus disease 2019 (COVID-19). Predictors of worse outcomes were older age and end-organ disease (particularly pulmonary hypertension) whereas treatment with hydroxycarbamide was protective.[97] There was a lack of matched controls to comment on Intensive Care Unit admission, but initial data suggest that there may be a greater risk of critical illness in SCD.[97] As for the pediatric population, COVID-19 seemed to cause few serious complications in children with SCD, with very few deaths reported.[98] Interestingly, in most studies, compared to HbSS, HbSC was not associated with a decreased risk of hospitalization or death.[97]

SARS CoV-2 has been shown to precipitate endothelial dysfunction,[99] and this alongside hypoxia and cytokine release could suggest a theoretical trigger for vaso-occlusion, although this did not seem to occur in practice.[100] During the pandemic there were significantly fewer ACS episodes reported, perhaps due to a reduction in all-cause respiratory infection due to public health measures including social distancing.[101] Equally, ACS related to COVID-19 did not seem to be associated with a worse prognosis compared to non-COVID ACS.[101]

The principles of management of COVID-19 in SCD are similar to those for non-SCD COVID-19 patients, with the addition of supportive transfusion and early use of antiviral agents and discussion with critical care if necessary.[96] Corticosteroids should be used with caution because of their association with complications in SCD, including acute pain and intracranial hemorrhage.[102] COVID-19 vaccination is safe and effective in this group but there is a lower vaccine uptake than in the general population despite the risk of adverse outcomes from the condition. Reasons for this need further exploration.[103,104]

Other viral infections

Dengue virus is endemic to many areas of high SCD prevalence including the Caribbean, South America and areas of Africa.[105] Dengue infection carries an increased mortality up to 12.5% in SCD patients, compared to healthy counterparts, but evidence is largely from small-scale studies and case reports, limiting its reliability.[105] Surprisingly, the risk of death appears to be higher in patients with HbSC than in those with HbSS, at least in some countries such as Jamaica.[105] Complications of infections include bleeding and loss of capillary integrity. Patients with SCD may have increased vulnerability to dengue due to immunodeficiency, endothelial cell activation and reduced physiological reserve as a result of SCD end-organ damage.[107] A tetravalent vaccine is licensed but only for those who have confirmed previous infection due to the increased risk of severe dengue in those who were seronegative prior to vaccination.[108]

Both hepatitis B and C are major viral causes of chronic liver disease, transmitted through transfer of blood or bodily fluids. The cost of viral screening has resulted in the use of unsafe blood products in most of sub-Saharan Africa, such that the seroprevalence for hepatitis C virus is 17% in patients with SCD receiving multiple transfusions.[109] Hepatitis B vaccination is recommended (Table 1), but treatment of hepatitis C in this population is challenging due to ribavirin-related hemolysis and high costs.[107]

Cytomegalovirus is rarely clinically significant in immunocompetent individuals, but patients who may be future candidates for hematopoietic stem cell transplantation should receive cytomegalovirus-negative blood products where possible.[108] Epstein-Barr virus is usually an asymptomatic and self-limiting viral infection, especially in children;[82] however in SCD it can cause hemolytic anemia, splenic rupture and hemophagocytic lymphohistiocytosis.[103]

Parasitic infections

Malaria

Malaria infections caused by plasmodium parasites have been the leading cause of premature death in tropical regions for much of the last 5,000 years.[110] The protective effect of the carrier form of SCD, sickle cell trait, against malaria caused by *P. falciparum*, the most dangerous plasmodial species, has been well described through multiple studies and it is now accepted that the trait is more than 90% protective against severe forms and roughly 50% protective against uncomplicated episodes of *P. falciparum* malaria.[111] This protective effect has led to such strong positive genetic selection for the sickle mutation that, typically, more than one in every ten children in most malaria-endemic parts of Africa and India are born with sickle cell trait.[112,113]

Until recently, the relationship between SCD and malaria has been somewhat controversial, some arguing that the incidence of malaria is higher and some that it is lower among subjects with SCD than in those without.[114,115] Recent research now tells us that the answer is more nuanced. It is certainly true that patients with SCD are not completely resistant to malaria, and that if they do become infected the disease can rapidly become severe, most commonly through the development of catastrophic anemia.[115,116] However, a recent study has also shown that they are strongly resistant to the

Table 2. Summary of clinically important infectious diseases in sickle cell disease.

Pathogen	Structure	Transmission	Clinical presentation	Treatment**	Prophylaxis	References
Bacterial Infections						
Streptococcus pneumoniae	Encapsulated Gram-positive cocci	Respiratory droplet	ACS LRTI Meningitis Preceding or concomitant viral infection	Penicillins, erythromycin* empirically, followed by culture-guided choice of antimicrobial and supportive care	Vaccination: - Pneumococcal conjugate vaccine PCV13 at 12 weeks and 1 year of age - Pneumococcal polysaccharide vaccine (PPV23) at 2 years of age and every 5 years thereafter Antimicrobial prophylaxis*	19,21, 125,126
Haemophilus influenzae	Encapsulated Gram-negative coccobacillus	Respiratory droplet	ACS Meningitis Septicemia Pneumonia Epiglottitis Cellulitis Arthritis Osteomyelitis Pericarditis	Third-generation cephalosporin while awaiting culture and sensitivity results** In cases of meningitis, repeat lumbar puncture following treatment to ensure sterility	Vaccination: - Conjugate Hib vaccine at 8,12 and 16 weeks and 1 year Antimicrobial prophylaxis*	34,92, 127,128
Chlamydia pneumoniae	Intracellular Gram-negative bacillus	Respiratory droplet	ACS Otitis media Bronchitis Sinusitis Myocarditis	Macrolides, tetracyclines	IPC measures Antimicrobial prophylaxis*	21,37
Neisseria meningitidis	Encapsulated Gram-negative coccus	Respiratory droplet	CNS infection (meningitis)	Third-generation cephalosporin, penicillins* (although penicillin resistance is a growing challenge)	Vaccination: - MenB (8 weeks, 16 weeks, 1 year) - Hib/MenC (combined booster at 1 year) - MenACWY (2 doses at least 4 weeks apart during the first year plus a booster dose 8 weeks after vaccines scheduled at 1 year of age***) Antimicrobial prophylaxis*	63,71,129
Staphylococcus aureus	Gram-positive coccus	Direct contact	Osteomyelitis	IV antibiotics guided by sensitivities and local guidelines. Surgical referral for source control if infection remains after 4-6 weeks of antibiotics.	IPC measures Systemic antimicrobials prior to any elective bone or joint surgery MRSA decolonization if to undergo surgery	48,130
Salmonella spp.	Gram-negative bacillus *Salmonella typhi* – only encapsulated species	Fecal-oral	Osteomyelitis	IV β-lactams/quinolones for 4-6 weeks if osteomyelitis Surgical referral for source control	IPC measures Antimicrobials prior to any elective bone or joint surgery No evidence for salmonella vaccines	56,131

Continued on following page.

Pathogen	Structure	Transmission	Clinical presentation	Treatment**	Prophylaxis	References
Viral Infections						
Parvovirus B19	Small linear single-stranded DNA erythrovirus	Droplet or vertical transmission	Aplastic crisis: fever, pain, symptomatic anemia	Transfusion and supportive care	Respiratory droplet IPC precautions	83,85
Human immunodeficiency virus	Single-stranded RNA enveloped lentivirus	Transfer of bodily fluids or sexual transmission, vertical transmission	Variable clinical presentation, can be asymptomatic	HAART therapy	Education on transmission Blood product screening PEP/PrEP	87,89,132
Influenza	Single-stranded RNA virus	Respiratory droplet, aerosol	LRTI, ACS, can present gastrointestinal manifestations in pediatric population	Antiviral agents if clinical suspicion of H1N1 infection (e.g. Osteltamivir) as per local advice, oxygen therapy, respiratory supportive care Involvement of respiratory and critical care colleagues if necessary	Annual influenza vaccination from 6 months of age	18,92
SARS-CoV-2 (COVID-19)	Positive-sense single-stranded coronavirus	Respiratory droplet, aerosol	Fatigue, fever, abdominal pain, anosmia Infective respiratory syndrome ranging from URTI to ACS, ARDS	Blood transfusions, antiviral agents, oxygen therapy and supportive care Involvement of respiratory and critical care colleagues if necessary	Vaccination and booster doses as per current local guidance. Non-pharmacological social isolation precautions in pandemic scenarios	94,98
Dengue virus	Single-stranded, positive-sense RNA flavivirus	Bite from an infected *Aedes aegypti* or *Aedes albopictus* mosquito	Headaches, fever, abdominal pain, hemorrhage, myalgia, and loss of capillary integrity	Supportive care including transfusion if necessary	Non-pharmacological mosquito repellent measures Vaccination in those >4 years traveling to endemic areas with confirmed previous infection	103
Hepatitis B virus	Enveloped DNA virus	Transfer of bloods/ bodily fluids or sexual transmission	Acute or chronic liver dysfunction	Nucleoside analogs	Hepatitis B vaccination as per local vaccination schedule, viral screening of blood products	92,103
Hepatitis C virus	Enveloped, positive-sense single-stranded RNA virus	Transfer of blood/ bodily fluids	Acute or chronic liver dysfunction	Ribavirin-free antiviral regimes	IPC measures, viral screening of blood products	103,107
Epstein-Barr virus (infectious mononucleosis)	Double-stranded DNA virus	Transfer of bodily fluids, including saliva.	Often asymptomatic/ self-limiting. Fever, lymphadenopathy, pharyngitis. Can cause splenic rupture, thrombocytopenia, agranulocytosis, hemolytic anemia, and HLH in SCD.	Supportive care, avoidance of contact sports for at least 1 month following infectious mononucleosis	IPC measures, avoiding infectious contacts	82,103,133

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Pathogen	Structure	Transmission	Clinical presentation	Treatment**	Prophylaxis	References
Parasitic Infections						
Intestinal helminth infections	Large multicellular macroparasitic worms	Fecal-oral	Iron deficiency, exacerbation of anemia	Transfusion support/ iron supplementation to treat anemia. Routine treatment with anti-helminthic medication as per local guidance.	Water and food de-contamination in developing countries where this is not standard practice Encourage good hand hygiene	123,124,134
Protozoan infections	Unicellular parasitic organisms	Fecal-oral	Protozoal colitis, exacerbation of anemia	Supportive care and rehydration to replace gastrointestinal losses Transfusional support as required Specific anti-protozoal therapy as per microbiology guidance	Water and food de-contamination in developing countries where this is not standard practice Encourage good hand hygiene	135
Plasmodium spp. infections (malaria)	Unicellular parasites of the Plasmodiidae family	Bite of infected female Anopheles mosquito	Spectrum of disease from fever, malaise and headache to severe clinical syndrome with profound anemia and organ dysfunction	Supportive care Antimalarial agents	Non-pharmacological mosquito repellent measures Malaria chemoprophylaxis Malaria vaccine	120,121

All vaccination and management recommendations as per UK immunization schedule and NICE guidelines[43] at the time of writing, but may vary between countries and be subject to change. Antimicrobial choices should be guided by local microbiology advice and culture sensitivities. Antimicrobial prophylaxis in sickle cell disease (SCD) should be for all patients up to 5 years old with the option to continue. *Erythromycin used in cases of penicillin allergy. **Advice should always be sought from local guidelines and microbiologists when choosing an antibiotic. *** Based on age of presentation with SCD, this is presuming a diagnosis is made before 1 year old. ACS: acute chest syndrome; LRTI: lower respiratory tract infection; Hib: *Haemophilus influenzae* type B; IPC: infection prevention and control; CNS: central nervous system; MenB: meningitis B vaccine; MenC: meningitis C vaccine; Men ACWY: meningitis ACWY vaccine; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*; HAART: highly active antiretroviral therapy; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 2019; URTI: upper respiratory tract infection; ARDS: acute respiratory distress syndrome; HLH: hemophagocytic lymphohistiocytosis.

majority of malaria strains, and that only a minor subgroup of parasites that are characterized by three specific genetic mutations can break through this resistance,[117] a discovery that has prompted a new wave of basic science research in this area.[118,119]

In spite of this fascinating scientific discovery, it is clear that malaria is a leading cause of morbidity and death among children born with SCD in sub-Saharan Africa,[115,120] and that it is very important from a clinical perspective that, wherever possible, patients should avoid becoming infected by malaria through mosquito avoidance measures and through the use of malaria chemoprophylaxis. In this regard, the development of anti-malarial drug resistance in recent decades, in parallel with the potential side effects of many antimalarial drugs, means that the options are becoming increasingly limited. Guidelines are inconsistent between African countries and further trials to identify the most appropriate agents are urgently needed. It is therefore hoped that children living in Africa with SCD will benefit disproportionately from R21/Matrix-M, the first effective malaria vaccine[121] to be licensed for use on the African continent. When SCD patients who reside in non-malaria endemic countries travel to malaria-endemic regions they should follow the same travel advice for malaria prevention that would apply to any other traveler from their country of residence.

Intestinal parasites

Intestinal parasitic (helminthic and protozoal) infections pose a significant risk to those with SCD (Figure 1). Parasitic diseases are endemic in many regions where SCD is prevalent. Iron deficiency secondary to malabsorption and bleeding in those infected can exacerbate anemia in SCD although they may reduce the incidence of some complications.[122] A study in Nigeria demonstrated that those with intestinal parasitic infection and SCD had a lower hematocrit than SCD controls, but did not comment on the statistical significance of this.[123] A more recent Nigerian study found a significantly lower median hemoglobin concentration in patients with intestinal helminth infections but did not find a significant difference in episodes of pain.[124] Estimating the prevalence of these infections is challenging without widespread screening.

Summary

Table 2 provides a overview of the bacterial, viral and parasitic infectious diseases that are important in SCD, summarizing the pathogens involved, their transmisson, clinical presentation, treatment and prophylaxis.[125-135] People with SCD have increased susceptibility to infection, through functional asplenia, immune dysregulation, chronic inflammation, repeated hospital admissions and the consequences of end-organ damage. Infection precipitates many of the acute complications of SCD, and is likely to be responsible for a lot of the variability that characterizes the condition.[136] Children and those who live in low- and middle-income countries are most vulnerable to infective complications, where access to care and appropriate treatment is limited, creating a global disparity in the outcomes of infections in SCD. While the development of novel curative approaches, such as gene therapy, is encouraging, more urgent action is needed to ensure that all SCD patients have access to basic medical care.[137]

The severity and prevalence of infections varies widely according to age, geographical location and the degree of socio-economic deprivation, highlighting the need for targeted intervention. Optimal management involves early testing to guide antimicrobial agents. Antimicrobial resistance is a growing challenge and antibiotic stewardship is key. Prevention of infection is important and requires a multi-modal approach.

The quality of evidence is generally poor in this area. There are only a few recent studies, mostly focusing on Europe and the US. Nearly all the evidence arises from studies of SCA (HbSS), and while it is currently recommended that patients with other types of SCD follow the same guidelines, it is likely that there are important differences in the immune function and pattern of infection seen in other common types of SCD, such as HbSC disease and HbS/β thalassemia. For example, there is reasonable evidence that children with HbSC disease develop hyposplenism at an older age than those with SCA and should follow different guidelines for prophylactic penicillin.[138] Therefore, many questions relating to infections in SCD remain unanswered and further work is needed. Poor outcomes associated with infection in SCD are potentially modifiable with relatively cheap interventions focused on public health measures and the availability of antimicrobials.

Disclosures

No conflicts of interest to disclose.

Contributions

LEAS wrote most of the first draft of the manuscript. AM-N wrote the section on immune function. TNW wrote the section on malaria. DCR revised the initial draft of the manuscript. All authors edited and approved the final version of the manuscript.

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