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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 (ACS), 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 COVID19. 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 vaccinations, 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 *S. 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 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, 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 of both 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 focuses 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. After the introduction of antimicrobial prophylaxis and immunisations, 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 SCD

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 a major cause of early childhood mortality.[12] Twenty years later, the Cooperative Study of Sickle Cell Disease found the annual incidence of pneumococcal sepsis in SCD to be 10 per 100 person-years, observed in 335 children under the age of three 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, greatly reducing morbidity and mortality in children with SCD.[14] Today, antibiotic prophylaxis remains a cornerstone of treatment in the under-five population with SCA, although there is a need for more evidence on its use 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 includes 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 (VOC) 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 +/- 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 (Table 2) it is important that appropriate infection prevention and control (IPC) 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 anerobe, gram-positive bacterium. *S. pneumoniae* is a commensal organism of the upper respiratory tract in healthy individuals, causing community acquired pneumonia when migrating to the lungs[19] Pneumococcal infection is a predominant cause of mortality amongst children with SCD, due to its relative abundance and frequency of progression to septicemia (children <5 years with SCD are at a 400 fold risk[20]). Its associated clinical syndromes includes lower respiratory tract infection (LRTI), ACS, meningitis and overwhelming sepsis; preceding or concomitant viral infection is a common feature.[21]

Hyposplenism predisposes towards 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 (PAFr). Before preventative measures were introduced, children with SCD were 30-600 times more likely to develop Invasive Pneumococcal Disease (IPD) than children without SCD[23] These numbers have significantly improved with the introduction of effective penicillin prophylaxis and the pneumococcal conjugate vaccine (PCV). IPD rates have decreased by up to 93.4% in children <5 years, 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 beta 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 (SSA) 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 which poses a respiratory threat in SCD is *Haemophilus influenzae*. Before the introduction of effective vaccination in 1992,[29] mortality from invasive Haemophilus 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 (URTI), 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 not been eradicated. A retrospective single centre study from the United States (US) identified an incidence of 0.58/1000 person-years for children with SCD aged 0 to 18 years, but no deaths.[31] In

contrast, another US centre 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 SSA die before the diagnosis is confirmed.[33] Improved access to vaccines in these low and middle income countries (LMICs) 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 which has a propensity for infecting 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 *C. pneumoniae* PCR positivity found in 13-14% of cases.[36,37] A positive PCR in ACS was associated with older age, lower hemoglobin and chest pain. Despite its proposed association with endothelial inflammation, Goyal et al (2004)[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 beta-lactam resistance,[39] making treatment increasingly difficult (Table 2).

Mycoplasma

Mycoplasma pneumoniae is a small bacterium, lacking a cell wall, which is a common respiratory pathogen in all populations, accounting for 10-40% cases of all 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.[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 SCD

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. 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 immunisation remains one of the most effective defence strategies against respiratory bacterial infections in SCD, as part of the childhood immunisation schedule (Table 1). Vaccine uptake however, has been reported to vary widely geographically (46-95%)[43–45] and further work is needed to ascertain vaccine response 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.[46] Penicillin prophylaxis (or erythromycin in penicillin allergy) protects against

pneumococcal infection,[47] 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 morbidity. Those 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.[48] 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,[49] although 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 period of about four years, 12% developed osteomyelitis. Two organisms account for most of the infections .[50]

Staphylococcus aureus

S. 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 SSA and the Middle East.[51,52] 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.[53] Bone is a dynamic organ, especially in SCD with increased marrow turnover, and it serves as an attractive target for bacteria. *S. aureus* species possess microbial surface components recognising adhesive matrix molecules (MSCRAMMs) which aid their invasion of bone and pathogenesis in osteomyelitis.[54] Increasing challenges in treating *S. aureus* are mainly due to resistance including methicillin-resistant species (MSRA). Mechanisms of treatment failure are polyfactorial resulting from bacterial and host factors, but prompt initiation and escalation of treatment is vital in these cases.[55]

Salmonella spp

Salmonella species are gram negative bacilli, of which *Salmonella typhi* is the only encapsulated organism.[56] In the post-pneumococcal vaccine era, non-typhoidal Salmonella spp were the leading cause of invasive bacterial infection in a European pediatric SCD population.[53] Salmonella bacteremia is associated with 77% incidence of osteomyelitis in SCD. [57] Salmonella infections are more prevalent in US and European regions, but some controversy exists and further updated work is needed to confirm this. [51,52,58] Proposed mechanisms for increased salmonella vulnerability in this group include increased intestinal permeability due to hypoxic injury during VOC or alterations in gut microbiota contributing to increased risk of gut translocation.[59] 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.[60]

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*,[61] *Klebsiella,*[61] *Bacteroides fragilis*[62], *Enterobacter cloacae*[63] and *Pseudomonas aeruginosa,*[63] 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[64] and a Buruli skin ulcer caused by *Mycobacterium ulcerans.*[65]

Treatment of osteomyelitis in SCD

Management of osteomyelitis in SCD needs to be multi-disciplinary 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.[66] Current consensus is that targeted IV antibiotic therapy for 4-6 weeks is important for good outcomes.[48] A Cochrane Review in 2019[67] 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.[68]

Other infectious syndromes in SCD

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.[69] 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 CNS via the ethmoid bone or the bloodstream and has an overall mortality of 13% in the general population.[69] In a study from a US national database of 533 SCD admissions from 2016-2019, none had culture-positive *N.meningitidis.*[70] This is perhaps due to efficacy in vaccination (Table 1) or early initiation in treatment resulting in poor culture yield. 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.[48] Penicillin resistance is an issue with *N.meningitidis* and third generation cephalosporins tend to be the treatment of choice (Table 2).[71]

Urinary tract infections

Urinary tract infections (UTI) 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 UTI, with *Escherichia coli* accounting for most of the cases, which is similar to the incidence in the non-SCD population.[72] Studies from SSA generally suggest higher rates of urine infections in SCD; for example, a study from Tanzania found that about 29% of girls and 14% of boys had a UTI based on dipstick testing, with *E. coli* being the most commonly isolated organism, and *Klebsiella, Staphylococcus, Proteus* and *Pseudomonas* species also identified[73]. Similarly a

cross-sectional study from Zambia found that 25% patients with SCD had bacteriuria[74]. Based on these limited data, febrile patients with SCD should be tested for possible UTIs, and if present, these should be investigated and treated in the usual way.

Bacterial prophylaxis in SCD

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 continue. A randomised, double-blind , placebo-controlled trial of penicillin in children with SCA under the age of three 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 age 5 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.[75,76] 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 continue. For example, in the USA most guidelines suggest it can stop at the age of 5 years,[77] whereas in the UK lifelong penicillin is recommended. Other countries, such as France, typically stop penicillin when children start secondary school at around the age of 10 years, and in many SSA countries use is largely determined by availability and affordability, meaning that many patients do not get it.[78] 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.[78] 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 infection prevention strategies. A study of Ugandan children showed that initiating hydroxycarbamide reduced infections by 60% ($p<0.001$),[79] and data from the REACH trial showed a reduction in both malarial and non-malarial infections[80] 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.[81] 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 pre-dispose 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.[82] 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.[83] Treatment centres 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.[84,85] 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.[86]

The seroprevalence of parvovirus in studies varies widely based on geographical location, socioeconomic status, age at serological testing and transfusion history.[83] A US study in children measured the incidence at 11.3 per 100 patient years.[85] No commercially available vaccine currently exists.

HIV

Human Immunodeficiency Virus (HIV) has a prevalence of up to 11.5% in some SCD populations, compared to 0.7% worldwide.[87,88] This is largely explained by the geographical overlap in SSA countries where the prevalence of both conditions is high and access to care for both is limited.[87] 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 AIDS.[87] 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.[89] Both conditions independently increase risk of stroke, avascular necrosis, pulmonary hypertension and co-existence increases risk of HIV and SCD complications.[87] Some case reports suggest that antiretroviral therapy (ART) may induce acute painful episodes in SCD, but it is unclear whether these medications cause this directly or indirectly via cytokines.[90]

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 to be hospitalised with influenza than healthy counterparts although there does not seem to be an increased risk of admission to intensive care or death.[91] ACS guidelines[18] recommend routine nasopharyngeal aspirate for influenza A (including 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 LRTI.[56] It is generally recommended that people with SCD receive annual vaccination against influenza where this is available, although more evidence is needed about the efficacy of this in SCD.[92,93]

COVID-19

Underlying cardiopulmonary comorbidities and immunocompromise make those with SCD vulnerable to respiratory SARS-CoV-2 infection. In systematic review and meta-analysis,[94] it was shown that when adjusted for confounders, SCD patients were more likely to die (OR 1.86; 95% CI 1.30-2.66) and be hospitalised (OR 5.44; 95% CI 1.55-19.13) with COVID-19. Predictors of worse outcomes were older age, end-organ disease (particularly pulmonary hypertension) whereas treatment with hydroxycarbamide was protective.[95] There was a lack of matched controls to comment on ICU admission, but initial data suggests there may be a greater risk of critical illness in SCD[95]. As for the pediatric population, COVID-19 seemed to cause few serious complications in children with SCD, with very few deaths reported.[96] Interestingly, in most studies, HbSC was not associated with a decreased risk of hospitalization or death compared to HbSS[95].

SARS CoV-2 has been shown to precipitate endothelial dysfunction,[97] and this alongside hypoxia and cytokine release could suggest a theoretical trigger for vaso-occlusion, although this did not seem to occur in practice.[98] During the pandemic there were significantly fewer ACS episodes reported, perhaps due to all-cause respiratory infection reduction due to public health measures including social distancing.[99] Equally ACS related to COVID-19 infection did not seem to be associated with a worse prognosis compared to non-COVID ACS.[99]

Principles of management are similar to the non-SCD COVID-19 patient, with the addition of supportive transfusion and early use of antiviral agents and discussion with critical care if necessary.[94] Corticosteroids should be used with caution due to association with complications in SCD, including acute pain and intracranial hemorrhage.[100] 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.[101,102]

Other Viral Infections

Dengue virus is endemic to many areas of high SCD prevalence including the Caribbean, South America and areas of Africa.[103] 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.[103] Surprisingly, the risk of death appears to be higher in patients with HbSC compared to HbSS, at least in some countries such as Jamaica.[104] 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 due to SCD end organ damage.[104]A tetravalent vaccine is licensed but only in those who have confirmed previous infection due to the increased risk of severe dengue in those who were seronegative prior to vaccination.[105]

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 resulting in a seroprevalence for HCV of 17% in patients with SCD receiving multiple transfusions.[106] Hepatitis B vaccination is recommended (Table 1), but treatment of HCV in this population is challenging due to ribavirin-related hemolysis and high costs.[107]

Cytomegalovirus (CMV) is rarely clinically significant in immunocompetent individuals, but patients who may be future candidates for hematopoietic stem cell transplantation should receive CMV-negative blood products where possible.[108] Epstein Barr Virus (EBV) is usually asymptomatic and self-limiting viral infection especially in children,[82] however in SCD it can

cause hemolytic anemia, splenic rupture and hemophagocytic lymphohistiocytosis (HLH) (Table 2).[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 5000 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 respectively.[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 majority of malaria strains, and that only a minor sub-group of parasites that are characterised 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 SSA,[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 licenced for use on the African continent. Where 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 traveller 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 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 in 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

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 which characterises the condition.[136] Children and those who live in LMICs 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. Whilst 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 socioeconomic 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 whilst 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 thalassaemia. 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.

References

1. Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. N Engl J Med. 2017;376(16):1561-1573.

2. King H, Shumacker HB. Splenic Studies: I. Susceptibility to Infection after Splenectomy Performed in Infancy. Ann Surg. 1952;136(2):239-242.

3. Pearson HA, Gallagher R, Chilcote R, et al. Developmental pattern of splenic dysfunction in sickle cell disorders. Pediatrics. 1985;76(3):392-397.

4. Diggs LW. Siderofibrosis of the spleen in sickle cell anemia. J Am Med Assoc 1935;104(7):538–541.

5. Nardo-Marino A, Glenthøj A, Brewin JN, et al. The significance of spleen size in children with sickle cell anemia. Am J Hematol. 2022;97(12):1520-1528.

6. Rogers ZR, Wang WC, Luo Z, et al. Biomarkers of splenic function in infants with sickle cell anemia: baseline data from the BABY HUG Trial. Blood. 2011;117(9):2614-2617.

7. Cottas de Azevedo JT, Malmegrim KCR. Immune mechanisms involved in sickle cell disease pathogenesis: current knowledge and perspectives. Immunol Lett. 2020;224:1-11.

8. Tubman VN, Maysonet D, Estrada N, et al. Unswitched memory B cell deficiency in children with sickle cell disease and response to pneumococcal polysaccharide vaccine. Am J Hematol. 2024;99(6):1084-1094.

9. Telfer P, Coen P, Chakravorty S, et al. Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London. Haematologica. 2007;92(7):905-912.

10. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. Blood. 2010;115(17):3447-3452.

11. Wierenga KJ, Hambleton IR, Lewis NA. Survival estimates for patients with homozygous sickle-cell disease in Jamaica: a clinic-based population study. Lancet. 2001;357(9257):680-683.

12. Pearson HA, Spencer RP, Cornelius EA. Functional asplenia in sickle-cell anemia. N Engl J Med. 1969;281(17):923-926.

13. Gaston M, Rosse WF. The cooperative study of sickle cell disease: review of study design and objectives. Am J Pediatr Hematol Oncol. 1982;4(2):197-201.

14. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med. 1986;314(25):1593-1599.

15. Facchin A, Bui S, Leroux S, et al. Variability of ciprofloxacin pharmacokinetics in children: impact on dose range in sickle cell patients. J Antimicrob Chemother. 2018; 73(12):3423-3429.

16. A Sickle Crisis? National Confidential Enquiry into Patient Outcome and Death. 2008. www.ncepod.org.uk. (accessed May 16, 2024)

17. Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and Outcomes of the Acute Chest Syndrome in Sickle Cell Disease. N Engl J Med. 2000;342(25):1855-1865.

18. Howard J, Hart N, Roberts-Harewood M, Cummins M, Awogbade M, Davis B. Guideline on the management of acute chest syndrome in sickle cell disease. Br J Haematol. 2015;169(4):492-505.

19. Gonzales J, Chakraborty T, Romero M, et al. Streptococcus pneumoniae and its virulence factors H2O2 and pneumolysin are potent mediators of the acute chest syndrome in sickle cell disease. Toxins (Basel). 2021;13(2):157.

20. Powars D, Overturf G, Turner E. Is there an increased risk of Haemophilus influenzae septicemia in children with sickle cell anemia? Pediatrics. 1983;71(6):927-931.

21. Wong W-Y, Overturf GD, Powars DR. Infection caused by Streptococcus pneumoniae in children with sickle cell disease: epidemiology, immunologic mechanisms, prophylaxis, and vaccination. Clin Infect Dis. 1992;14(5):1124-1136.

22. Miller ML, Gao G, Pestina T, Persons D, Tuomanen E. Hypersusceptibility to invasive pneumococcal infection in experimental sickle cell disease involves platelet-activating factor receptor. J Infect Dis. 2007;195(4):581-584.

23. Halasa NB, Shankar SM, Talbot TR, et al. Incidence of invasive pneumococcal disease among individuals with sickle cell disease before and after the introduction of the pneumococcal conjugate vaccine. Clin Infect Dis. 2007;44(11):1428-1433.

24. Assad Z, Michel M, Valtuille Z, et al. Incidence of acute chest syndrome in children with sickle cell disease following implementation of the 13-valent pneumococcal conjugate vaccine in France. JAMA Netw Open. 2022;5(8):e2225141.

25. Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa: a neglected cause of early childhood mortality. Am J Prev Med. 2011;41(6 Suppl 4):S398-405.

26. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010-2050: modelling based on demographics, excess mortality, and interventions. PLoS Med. 2013;10(7):e1001484.

27. Williams TN. Sickle Cell Disease in Sub-Saharan Africa. Hematol Oncol Clin North Am. 2016;30(2):343-358.

28. De Montalembert M, Abboud MR, Fiquet A, et al. 13-valent pneumococcal conjugate vaccine (PCV13) is immunogenic and safe in children 6-17 years of age with sickle cell disease previously vaccinated with 23-valent pneumococcal polysaccharide vaccine (PPSV23): Results of a phase 3 study. Pediatr Blood Cancer. 2015;62(8):1427-1436.

29. Davies JM, Lewis MPN, Wimperis J, Rafi I, Ladhani S, Bolton-Maggs PHB. Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen: Prepared on behalf of the British Committee for Standards in Haematology by a Working Party of the Haemato-Oncology Task Force. Br J Haematol. 2011;155(3):308-317.

30. Gill FM, Sleeper LA, Weiner SJ, et al. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative Study of Sickle Cell Disease. Blood. 1995;86(2):776-783.

31. Yee ME, Bakshi N, Graciaa SH, et al. Incidence of invasive *Haemophilus influenzae* infections in children with sickle cell disease. Pediatr Blood Cancer. 2019;66(6):e27642.

32. Ellison AM, Ota KV, McGowan KL, Smith-Whitley K. Epidemiology of bloodstream infections in children with sickle cell disease. Pediatr Infect Dis J. 2013;32(5):560-563.

33. Williams TN, Uyoga S, Macharia A, et al. Bacteraemia in Kenyan children with sickle-cell anaemia: a retrospective cohort and case-control study. Lancet. 2009;374(9698):1364-1370.

34. Allali S, Chalumeau M, Launay O, Ballas SK, de Montalembert M. Conjugate Haemophilus influenzae type b vaccines for sickle cell disease. Cochrane Database System Rev. 2018;8(8):CD011199.

35. Campbell LA, Kuo C. Chlamydia pneumoniae-an infectious risk factor for atherosclerosis? Nat Rev Microbiol. 2004;2(1):23-32.

36. Miller ST, Hammerschlag MR, Chirgwin K, et al. Role of Chlamydia pneumoniae in acute chest syndrome of sickle cell disease. J Pediatr. 1991;118(1):30-33.

37. Dean D, Neumayr L, Kelly DM, et al. Chlamydia pneumoniae and acute chest syndrome in patients with sickle cell disease. J Pediatr Hematol Oncol. 2003;25(1):46-55.

38. Goyal M, Miller ST, Hammerschlag MR, et al. Is Chlamydia pneumoniae infection associated with stroke in children with sickle cell disease? Pediatrics. 2004;113(4):e318-e321.

39. Chlamydia pneumoniae Infection | CDC. https://www.cdc.gov/pneumonia/atypical/cpneumoniae/index.html 2023. accessed May 15, 2024.

40. Ferwerda A, Moll HA, de Groot R. Respiratory tract infections by Mycoplasma pneumoniae in children: a review of diagnostic and therapeutic measures. Eur J Pediatr. 2001;160(8):483-491.

41. Neumayr L, Lennette E, Kelly D, et al. Mycoplasma disease and acute chest syndrome in sickle cell disease. Pediatrics. 2003;112(1 Pt 1):87-95.

42. Shulman ST, Bartlett J, Clyde WA, Ayoub EM. The unusual severity of Mycoplasmal pneumonia in children with sickle-cell disease. N Engl J Med. 1972;287(4):164-167.

43. Chen C, Bakeera-Kitaka S, Mupere E, et al. Paediatric immunisation and chemoprophylaxis in a Ugandan sickle cell disease clinic. J Paediatr Child Health. 2019;55(7):795-801.

44. Gorham MW, Smith CR, Smith SK, Wong L, Kreze O. Vaccinations in sickle cell disease: An audit of vaccination uptake in sickle cell patients attending Newham University Hospital. Vaccine. 2015;33(38):5005-5011.

45. Jarovsky D, Bastos PR, de Matos SF, et al. Vaccination in pediatric patients with sickle-cell disease: uptake report and mini-review. J Trop Pediatr. 2022;68(3):fmac034.

46. Lebensburger JD, Howard T, Hu Y, et al. Hydroxyurea therapy of a murine model of sickle cell anemia inhibits the progression of pneumococcal disease by down-modulating E-selectin. Blood. 2012;119(8):1915-1921.

47. Pearson HA. Sickle cell anemia and severe infections due to encapsulated bacteria. J Infect Dis. 1977;136 Suppl:S25-30.

48. Sobota A, Sabharwal V, Fonebi G, Steinberg M. How we prevent and manage infection in sickle cell disease. Br J Haematol. 2015;170(6):757-767.

49. Berger E, Saunders N, Wang L, Friedman JN. Sickle cell disease in children: differentiating osteomyelitis from vaso-occlusive crisis. Arch Pediatr Adolesc Med. 2009;163(3):251-255.

50. Neonato MG, Guilloud-Bataille M, Beauvais P, et al. Acute clinical events in 299 homozygous sickle cell patients living in France. Eur J Haematol. 2000;65(3):155-164.

51. Burnett MW, MD JWB, Cook BA. Etiology of osteomyelitis complicating sickle cell disease. Pediatrics. 1998;101(2):296-297.

52. Thanni LO. Bacterial osteomyelitis in major sickling haemoglobinopathies: geographic difference in pathogen prevalence. Afr Health Sci. 2006;6(4):236-239.

53. Gaschignard J, Koehl B, Rees DC, et al. Invasive bacterial infections in children with sickle cell disease: 2014-2019. Pediatrics. 2023;152(4):e2022061061.

54. Kavanagh N, Ryan EJ, Widaa A, et al. Staphylococcal Osteomyelitis: Disease Progression, Treatment Challenges, and Future Directions. Clin Microbiol Rev. 2018;31(2):e00084-17.

55. Gimza BD, Cassat JE. Mechanisms of antibiotic failure during staphylococcus aureus osteomyelitis. Front Immunol. 2021;12:638085.

56. Ochocinski D, Dalal M, Black LV, et al. Life-threatening infectious complications in sickle cell disease: a concise narrative review. Front Pediatr. 2020;8:38.

57. Zarkowsky HS, Gallagher D, Gill FM, et al. Bacteremia in sickle hemoglobinopathies. J Pediatr. 1986;109(4):579-585.

58. Sadat-Ali M, Al-Umran K, Al-Habdan I, Al-Mulhim F. Ultrasonography: can it differentiate between vasoocclusive crisis and acute osteomyelitis in sickle cell disease? J Pediatr Orthop. 1998;18(4):552-554.

59. Lim SH, Methé BA, Knoll BM, Morris A, Obaro SK. Invasive non-typhoidal Salmonella in sickle cell disease in Africa: is increased gut permeability the missing link? J Transl Med. 2018;16(1):239.

60. Odey F, Okomo U, Oyo-Ita A. Vaccines for preventing invasive salmonella infections in people with sickle cell disease. Cochrane Database Syst Rev. 2018;12(12):CD006975.

61. Hashimi AZA, Fazari EA, Ward MA, et al. Predictors of developing a complex course of osteomyelitis in patients with sickle cell anaemia. Sultan Qaboos Univ Med J. 2024;24(1):58-62.

62. Bassam Hamieh N, Abdul Hamid Abou Layla H, Ali Ali R, Bayram Z, Bizri AR. Bacteroides fragilis acute hematogenous osteomyelitis in a young female with sickle cell disease. Case Rep Infect Dis. 2023;2023:6340222.

63. Khalife S, Hanna-Wakim R, Ahmad R, et al. Emergence of gram-negative organisms as the cause of infections in patients with sickle cell disease. Pediatr Blood Cancer. 2021;68(1):e28784.

64. Kooy A, de Heide LJ, ten Tije AJ, et al. Vertebral bone destruction in sickle cell disease: infection, infarction or both. Neth J Med. 1996;48(6):227-231.

65. Pszolla N, Sarkar MR, Strecker W, et al. Buruli ulcer: a systemic disease. Clin Infect Dis. 2003;37(6):e78-82.

66. Al Farii H, Zhou S, Albers A. Management of osteomyelitis in sickle cell disease. J Am Acad Orthop Surg Glob Res Rev. 2020;4(9):e20.

67. Marti-Carvajal AJ, Agreda-Perez LH. Antibiotics for treating osteomyelitis in people with sickle cell disease. Cochrane Database Syst Rev. 2019;10(10):CD007175.

68. Chekroun M, Chérifi H, Fournier B, et al. Oral manifestations of sickle cell disease. Br Dent J. 2019;226(1):27-31.

69. Nguyen N, Ashong D. Neisseria meningitidis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/books/NBK549849/ (accessed 16 May, 2024).

70. Sharma A, Alavi A, Woldie IL, Singh V. National burden of encapsulated bacterial infections in sickle cell disease. Blood. 2022;140(Supplement 1):5148-5149.

71. Feldman C, Anderson R. Meningococcal pneumonia: a review. Pneumonia (Nathan). 2019;11(1):3.

72. Patel N, Farooqi A, Callaghan M, Sethuraman U. Urinary Tract Infection in Febrile Children with Sickle Cell Disease Who Present to the Emergency Room with Fever. J Clin Med. 2020;9(5):1531.

73. Sangeda RZ, Yohana J, Jonathan A, Manyanga VP, Soka D, Makani J. Prevalence of urinary tract infections and antibiogram of bacteria isolated from children with sickle cell disease in Tanzania. Cureus. 2024;16(4):e58786.

74. Musonda T, Zulu M, Samutela M, et al. Leucocytosis and Asymptomatic Urinary Tract Infections in Sickle Cell Patients at a Tertiary Hospital in Zambia. Anemia. 2020;2:2020:3792728.

75. Faletta JM, Woods GM, Verter JI, et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia. J Pediatr. 1995;1279(5):685-690.

76. Adamkiewicz TV, Yee ME, Thomas S, et al. Pneumococcal infections in children with sickle cell disease before and after pneumococcal conjugate vaccines. Blood Adv. 2023;7(21):6751-6761.

77. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312(10):1033-1048.

78. Brown BJ, Madu A, Sangeda RZ, et al. Utilization of pneumococcal vaccine and penicillin prophylaxis in sickle cell disease in three African countries: assessment among healthcare providers in SickleInAfrica. Hemoglobin. 2021;45(3):163-170.

79. Namazzi R, Bond C, Conroy AL, et al. Hydroxyurea reduces infections in children with sickle cell anemia in Uganda. Blood. 2024;143(14):1425-1428.

80. Aygun B, Lane A, Smart LR, et al. Hydroxyurea dose optimisation for children with sickle cell anaemia in sub-Saharan Africa (REACH): extended follow-up of a multicentre, open-label, phase 1/2 trial. Lancet Haematol. 2024;11(6)e425-e435.

81. Jayaraman S, Chalabi Z, Perel P, Guerriero C, Roberts I. The risk of transfusion-transmitted infections in sub-Saharan Africa. Transfusion. 2010;50(2):433-442.

82. Panicker J, Harris RG, Smith SD. Coinfection with Parvovirus B19 and Epstein Barr Virus in an adolescent with sickle cell disease manifesting as septic shock. Blood. 2011;118(21):4854.

83. Soltani S, Zakeri A, Tabibzadeh A, et al. A literature review on the parvovirus B19 infection in sickle cell anemia and β-thalassemia patients. Trop Med Health. 2020;48(1):96.

84. Ogunsile FJ, Currie KL, Rodeghier M, Kassim A, DeBaun MR, Sharma D. History of parvovirus B19 infection is associated with silent cerebral infarcts. Pediatr Blood Cancer. 2018;65(1):e26767.

85. Smith-Whitley K, Zhao H, Hodinka RL, et al. Epidemiology of human parvovirus B19 in children with sickle cell disease. Blood. 2004;103(2):422-427.

86. Majumdar S, Bean CJ, De Staercke C, et al. Parvovirus B19 infection in sickle cell disease: An analysis from the Centers for Disease Control haemoglobinopathy blood surveillance project. Transfus Med. 2020;30(3):226-230.

87. Owusu ED, Visser BJ, Nagel IM, Mens PF, Grobusch MP. The interaction between sickle cell disease and HIV infection: a systematic review. Clin Infect Dis. 2015;60(4):612-626.

88. World Health Organisation. Data on the size of the HIV epidemic. https://www.who.int/data/gho/data/themes/hiv-aids/data-on-the-size-of-the-hiv-aids-epidemic (2022, accessed May 16, 2024).

89. Lori F, Kelly LM, Foli A, Lisziewicz J. Safety of hydroxyurea in the treatment of HIV infection. Expert Opin Drug Saf. 2004;3(4):279-288.

90. Lowe SH, Prins JM, van der Lelie J, Lange JM. Does highly active antiretroviral therapy induce sickle cell crises? Aids. 2002;16(11):1572-1574.

91. Bundy DG, Strouse JJ, Casella JF, Miller MR. Burden of influenza-related hospitalizations among children with sickle cell disease. Pediatrics. 2010;125(2):234-243.

92. Scenario: Prevention of complications | Management | Sickle cell disease | CKS | NICE. https://cks.nice.org.uk/topics/sickle-cell-disease/management/prevention-of-complications/ (accessed May 16, 2024).

93. Kao CM, Lai K, McAteer JM, et al. Influenza vaccine effectiveness and disease burden in children and adolescents with sickle cell disease: 2012-2017. Pediatr Blood Cancer. 2020;67(8):e28358.

94. Michelon I, Vilbert M, Pinheiro IS, et al. COVID-19 outcomes in patients with sickle cell disease and sickle cell trait compared with individuals without sickle cell disease or trait: a systematic review and meta-analysis. EClinicalMedicine. 2023;66:102330.

95. Minniti CP, Zaidi AU, Nouraie M, et al. Clinical predictors of poor outcomes in patients with sickle cell disease and COVID-19 infection. Blood Adv. 2021;5(1):207-215.

96. Brousse V, Holvoet L, Pescarmona R, et al. Low incidence of COVID-19 severe complications in a large cohort of children with sickle cell disease: a protective role for basal interferon-1 activation? Haematologica. 2021;106(10):2746-2748.

97. Xu S-W, Ilyas I, Weng J-P. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. Acta Pharmacol Sin. 2023;44(4):695-709.

98. Alkindi S, Elsadek RA, Al-Madhani A, et al. Impact of COVID-19 on vasooclusive crisis in patients with sickle cell anaemia. Int J Infect Dis. 2021;106:128-133.

99. Dubois G, Virot E, Marie M, Poutrel S, Cannas G, Hot A. Impact of COVID-19 on incidence, clinical presentation, and prognosis of acute chest syndrome in patients with sickle cell disease. EJHaem. 2023;4(4):970-976.

100. Walter O, Cougoul P, Maquet J, et al. Risk of vaso-occlusive episode after exposure to corticosteroids in patients with sickle cell disease. Blood. 2022;139(26):3771-3777.

101. Han J, Zhang X, Molokie RE, et al. COVID-19 vaccination status and disease burden in patients with sickle cell disease. Br J Haematol. 2022;199(4):e21-e24.

102. Peng HK, Dombkowski KJ, Plegue MA, et al. COVID-19 Immunization Coverage Among People With Sickle Cell Disease. JAMA Netw Open. 2024;7(1):e2351618.

103. Sahu T, Pande B, Verma HK, et al. Infection and Potential Challenge of Childhood Mortality in Sickle Cell Disease: A Comprehensive Review of the Literature from a Global Perspective. Thalass Rep. 2023;13(3):206-229.

104. Rankine-Mullings A, Reid ME, Sang MM, Richards-Dawson M-A, Madden JMK-. A Retrospective Analysis of the Significance of Haemoglobin SS and SC in Disease Outcome in Patients With Sickle Cell Disease and Dengue Fever. EBioMedicine. 2015;2(8):937-941.

105. Elenga N, Nacher M, Trehan I. The Imperative of dengue vaccination for children with sickle cell disease. J Trop Pediatr. 2020;66(3):245-247.

106. Sonderup MW, Afihene M, Ally R, et al. Hepatitis C in sub-Saharan Africa: the current status and recommendations for achieving elimination by 2030. Lancet Gastroenterol Hepatol. 2017;2(12):910-919.

107. Suddle AR. Management of liver complications in sickle cell disease. Hematology. 2019;2019(1):345-350.

108. Win N. Blood transfusion therapy for haemoglobinopathies. In: Okpala IE, editor. Practical Management of Haemoglobinopathies 2004. Wiley. p99-106.

109. UK Health Security Agency. Routine childhood immunisations from 1 September 2023. *GOV.UK*. https://www.gov.uk/government/publications/routine-childhood-immunisation-schedule/routine-childhood-immunisations-from-february-2022-born-on-or-after-1-january-2020 (accessed May 16, 2024).

110. Kwiatkowski DP. How malaria has affected the human genome and what human genetics can teach us about malaria. Am J Hum Genet. 2005;77(2):171-192.

111. Taylor SM, Parobek CM, Fairhurst RM. Haemoglobinopathies and the clinical epidemiology of malaria: a systematic review and meta-analysis. Lancet Infect Dis. 2012;12(6):457-468.

112. Allison AC. Protection afforded by sickle-cell trait against subtertian malareal infection. Br Med J. 1954;1(4857):290-294.

113. Piel FB, Patil AP, Howes RE, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet. 2013;381(9861):142-151.

114. Mkombachepa M, Khamis B, Rwegasira G, Urio F, Makani J, Luzzatto L. High incidence of malaria in patients with sickle cell disease. Am J Hematol. 2022;97(10):E380-E381.

115. Uyoga S, Olupot-Olupot P, Connon R, et al. Sickle cell anaemia and severe Plasmodium falciparum malaria: a secondary analysis of the Transfusion and Treatment of African Children Trial (TRACT). Lancet Child Adolesc Health. 2022;6(9):606-613.

116. Henrici RC, Sautter CL, Bond C, et al. Decreased parasite burden and altered host response in children with sickle cell anemia and severe anemia with malaria. Blood Adv. 2021;5(22):4710-4720.

117. Band G, Leffler EM, Jallow M, et al. Malaria protection due to sickle haemoglobin depends on parasite genotype. Nature. 2022;602(7895):106-111.

118. Matuschewski K, Maier AG. Pas-de-deux: African Plasmodium falciparum adaptations to sickle hemoglobin. Trends Parasitol. 2022;38(4):267-268.

119. Gómez-Díaz E, Ranford-Cartwright L. Evolutionary race: Malaria evolves to evade sickle cell protection. Cell Host Microbe. 2022;30(2):139-141.

120. Williams TN, Obaro SK. Sickle cell disease and malaria morbidity: a tale with two tails. Trends Parasitol. 2011;27(7):315-320.

121. Duffy PE, Gorres JP, Healy SA, Fried M. Malaria vaccines: a new era of prevention and control. Nat Rev Microbiol. 2024 Jul 18. [Epub ahead of print].

122. Farid Z, Patwardhan VN, Darby WJ. Parasitism and anemia. Am J Clin Nutr. 1969;22(4):498-503.

123. Ahmed SG, Uraka J. Impact of intestinal parasites on haematological parameters of sickle-cell anaemia patients in Nigeria. East Mediterr Health J. 2011;17(9):710-713.

124. Onoh EA, Muoneke UV, Young EE, Nwatu BC. Effect of intestinal helminth infection on haemoglobin levels and frequency of vaso-occlusive crises in children with sickle cell anaemia (SCA) attending Federal Teaching Hospital, Abakaliki, Nigeria. PAMJ-CM. 2020;3(190):23506.

125. Navalkele P, Özgönenel B, McGrath E, Lephart P, Sarnaik S. Invasive Pneumococcal Disease in Patients With Sickle Cell Disease. J Pediatr Hematol Oncol. 2017;39(5):341-344.

126. Sickle Cell Society. Sickle cell disease in childhood: standards and recommendations for clinical care. 3rd Edition 2019. https:sicklecellsociety.org/wp-content/uploads/2019/11/SCD-in-Childhood_Final-version-1.pdf. (accessed May 16, 2024).

127. Anderson EC, Begg NT, Crawshaw SC, Hargreaves RM, Howard AJ, Slack MPE. Epidemiology of invasive Haemophilus influenzae infections in England and Wales in the pre-vaccination era (1990–2). Epidemiol Infect 1995;115(1):89-100.

128. Khattak ZE, Anjum F. Haemophilus influenzae Infection. In: StatPearls. Treasure Island (FL): StatPearls. Publishing 2024. https://www.ncbi.nlm.nih.gov/books/NBK562176/. (accessed May 16, 2024).

129. Cohn AC, MacNeil JR, Clark TA, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2013;62(RR-2):1-28.

130. Masters EA, Ricciardi BF, de Mesy Bentley KL, Moriarty TF, Schwarz EM, Muthukrishnan G. Skeletal infections: microbial pathogenesis, immunity and clinical management. Nat Rev Microbiol. 2022;20(7):385-400.

131. Anand AJ, Glatt AE. Salmonella osteomyelitis and arthritis in sickle cell disease. Semin Arthritis Rheum. 1994;24(3):211-221.

132. Belisário AR, Blatyta PF, Vivanco D, et al. Association of HIV infection with clinical and laboratory characteristics of sickle cell disease. BMC Infect Dis. 2020;20(1):638.

133. Lennon P, Crotty M, Fenton JE. Infectious mononucleosis. BMJ. 2015;350:h1825.

134. van den Enden E. Pharmacotherapy of helminth infection. Expert Opin Pharmacother. 2009;10(3):435-451.

135. Escobedo AA, Almirall P, Alfonso M, Cimerman S, Rey S, Terry SL. Treatment of intestinal protozoan infections in children. Arch Dis Child. 2009;94(6):478-482.

136. Rees DC, Brousse VAM, Brewin JN. Determinants of severity in sickle cell disease. Blood Rev. 2022;56:100983.

137. Piel FB, Rees DC, DeBaun MR, et al. Defining global strategies to improve outcomes in sickle cell disease: a Lancet Haematology Commission. Lancet Haematol. 2023;10(8):e633-e686.

138. Pourdieu C, El Hoss S, Le Roux E, et al. Relevance of Howell-Jolly body counts for measuring spleen function in sickle cell disease. Am J Hematol. 2023;98(5):E110-E112.

Tables

Scheduled administration	Immunisations
8 weeks	Diphtheria, tetanus, pertussis (whooping cough), polio, *H. influenzae* type b (Hib) and hepatitis B Meningococcal group B (MenB) Rotavirus gastroenteritis
12 weeks	Diphtheria, tetanus, pertussis, polio, Hib and hepatitis B Pneumococcal Conjugate Vaccine (PCV) Rotavirus
16 weeks	Diphtheria, Tetanus, Pertussis, Polio, Hib and Hepatitis B MenB
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 their first year)
1 Year	Hib and Meningococcal group C (MenC) PCV booster Measles, Mumps and Rubella (MMR) MenB 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 MMR Booster
12-13 years	Human Papilloma Virus (HPV) 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

Table 1: Recommended immunisations in SCD in the United Kingdom, assuming the patient has been diagnosed with SCD from birth, up to date at the time of writing. Adapted from NICE (2021)[92] and UK Health Security Agency (2023).[109]

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 following Antimicrobial prophylaxis*	[125] [21] [19],13-11-2024 05:01:00
Haemophilus influenzae	Encapsulated gram-negative coccobacilli	Respiratory droplet	ACS Meningitis Septicemia Pneumonia Epiglottitis Cellulitis Arthritis Osteomyelitis Pericarditis	Third-generation cephalosporin whilst awaiting culture and sensitivity results** Repeat LP in meningitis following treatment to ensure sterility	Vaccination: - Conjugate Haemophilus influenzae type B vaccine at 8,12 and 16 weeks and 1 year Antimicrobial prophylaxis*	[127] [34] [92] [128]
Chlamydia pneumoniae	Intracellular gram negative bacillus	Respiratory droplet	ACS Otitis media Bronchitis Sinusitis Myocarditis	Macrolides, tetracyclines	IPC measures Antimicrobial prophylaxis*	[37],21
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 (two 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*	[129],63,[71]
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 decolonisation if to undergo surgery	[48] [130]
Salmonella Spp.	Gram negative bacillus *Salmonella Typhi* – only encapsulated species	Faecal-oral	Osteomyelitis	IV beta 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	[131] [56]

Viral Infections						
Parvovirus B19	Small linear single-stranded DNA erythrovirus	Droplet or vertical transmission	Aplastic crisis: fever, pain, symptomatic anaemia	Transfusion and supportive care	Respiratory droplet IPC precautions	[83, 85]
HIV	Single strand 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 transmission, aerosol transmission	LRTI, ACS, can present gastrointestinal manifestations in paediatric 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]
COVID-19 (SARS-CoV-2)	Positive-sense single-stranded coronavirus	Respiratory droplet transmission, aerosol transmission	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, postive-sense RNA flavirus	Bite from an infected Aedes aegypti or Aedes albopictus mosquito	headaches, fever, abdominal pain, haemorrhage, myalgias, and loss of capillary integrity	Supportive care including transfusion if necessary	Non-pharmacological Mosquito repellent measures Vaccination in those >4 years travelling to endemic areas with confirmed previous infection	[103]
Hepatitis B	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	[103, 92]
Hepatitis C	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	[107, 103]
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, haemolytic anaemia, and HLH in SCD.	Supportive care, avoidance of contact sports for at least one month following infectious mononucleosis	IPC measures, avoiding infectious contacts	[82, 133, 103] 13-11-2024 05:01:00

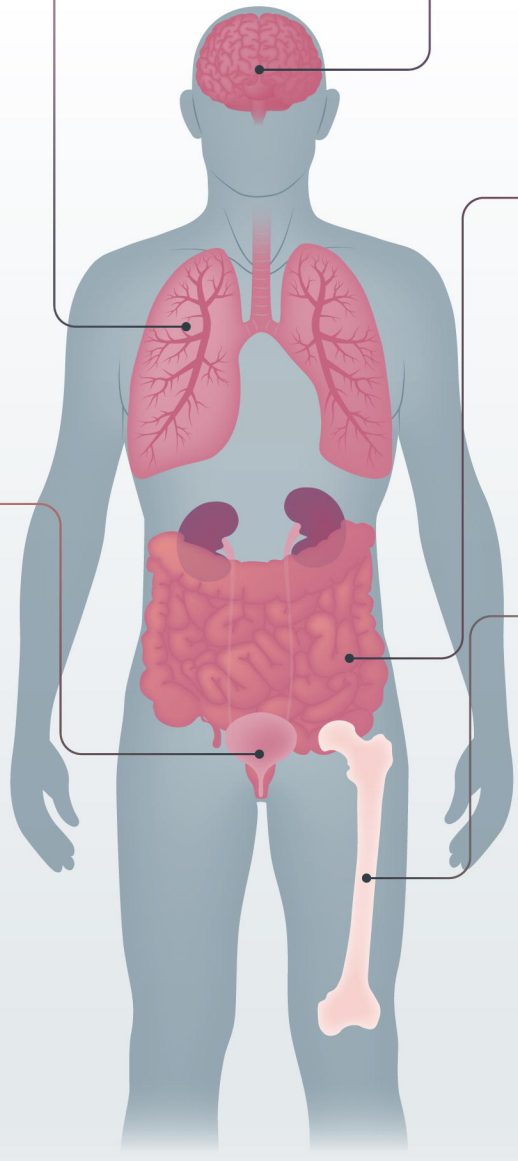
Parasitic Infections						
Intestinal Helminth Infections	Large multicellular macroparasitic worms	Faecal-oral	Iron deficiency, exacerbation of anaemia	Transfusion support/ iron supplementation to treat anaemia. Routine treatment with anti-helminthic medication as per local guidance.	Water and food de-contamination in developing countries where this is not standard practice Encourage good hand hygiene	[123,124,134]
Protozoan Infections	Unicellular parasitic organisms	Faecal-oral	Protozoal colitis, exacerbation of anaemia	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 anaemia and organ dysfunction	Supportive care Antimalarial agents	Non-pharmacological Mosquito repellent measures Malaria chemoprophylaxis Malaria vaccine	[120,121]

Table 2: Summary of clinically important infectious diseases in SCD. All vaccination and management recommendations as per UK immunisation schedule and NICE guidelines[63] at time of writing, but may vary between countries and be subject to change. Antimicrobial choices should be guided by local microbiology guidance and culture sensitivities. Antimicrobial prophylaxis in SCD should be for all patients up to 5 years with the option to continue. LRTI = lower respiratory tract infection, ACS=Acute Chest Syndrome, LP=lumbar puncture, CNS=central nervous system, MenB=meningitis B vaccine, MenC=meningitis C vaccine, Men ACWY=Meningitis ACWY vaccine VOC=vaso-occlusive crisis, IPC=infection prevention and control, MRSA=Methicillin-resistant Staphylococcus Aureus, ARDS=Acute respiratory distress syndrome, HIV=Human Immunodeficiency Virus, HAART=highly active antiretroviral therapy, PEP=Post exposure prophylaxis, PrEP=Pre exposure prophylaxis, HLH=haemophagocytic lymphohistiocytosis.

*Erythromycin used in penicillin allergy.
** Advice should always be sought from local guidelines and microbiologist when seeking choice of antibiotic.
*** Based on age of presentation with SCD, this is presuming diagnosis is made <1year

Figure Legend

Figure 1: Diagrammatic overview of key infections in sickle cell disease by organ system. EBV=Epstein-Barr Virus, CMV=cytomegalovirus, HIV=Human Immunodeficiency Virus.



Respiratory tract infections

- *Neisseria meningitides*
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Chlamydia pneumoniae*
- *Mycoplasma pneumoniae*

Malaria

- *Plasmodium vivax*
- *Plasmodium falciparum*
- *Plasmodium ovale*
- *Plasmodium malariae*

Urinary tract infections

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Candida albicans*
- *Enterococcus*
- *Enterococcus faecalis*
- Urinary schistosomiasis

Viral infections

- Parvovirus B19
- EBV
- CMV
- HIV
- Flu (H1N1)
- COVID-19
- Dengue
- Hepatitis

CNS infection

- *Neisseria meningitides*
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

Gastrointestinal parasitic infections

Helminths
- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Trichuris trichiura*
- *Strongyloides stercoralis*

Protozoa
- *Entamoeba histolytica*
- *Entamoeba coli*
- *Giardia lamblia*

Osteomyelitis/septic arthritis

- *Staphylococcus aureus*
- *Salmonella spp*

Common causes of bacteremia

Children
- *Streptococcus pneumoniae*
- Non-typhi *Salmonella* species
- *Haemophilus influenzae*
- *Acinetobacter* species
- *Escherichia coli*

Adults
- *Staphylococcus aureus*
- *Escherichia coli*
- Healthcare associated infections