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Infections and Sickle Cell Disease in Children

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Abstract

Introduction: Children with major sickle cell syndromes (MCS) are particularly vulnerable to infections, which can compromise their life expectancy and quality of life. Our objective was to study the profile of these infections in children followed in a specialized unit within an urban pediatric hospital, and more specifically, to describe the sociodemographic and epidemiological aspects, analyze the clinical, microbiological, and evolutionary profiles, and investigate associated factors. **Materials and Methods**: In a retrospective, descriptive, and analytical study conducted at the Outpatient Unit for Children and Adolescents with Sickle Cell Disease (USAD) of the Albert Royer National Children's Hospital in Dakar, Senegal. We included children under 16 years of age who were being treated for sickle cell disease and who experienced infectious episodes between January 2 and December 31, 2023. Those whose infections were not documented or whose records could not be located were not included. Data were analyzed using R software, version 4.4.1, and Excel Professional Plus 2021. **Results**: At the end of our study, we recorded a total of 4654 consultations, including 1785 for emergencies and 508 for infections. Infections represented 28.46% of emergency visits and 10.92% of consultations in the Ambulatory Healthcare Unit for Children and Teenagers (USAD). However, 280 (55.1%) met our inclusion criteria. Males were predominant (53.92%), with a male-to-female ratio of 1.15. The mean age was 109.88 ± 108 months, and 41.87% were between 5 and 10 years old. The homozygous SS form was the most frequent (93.63%), and the mean baseline hemoglobin level was 7.84 g/dL. 90.73% of the children were up-to-date with their Expanded Program on Immunization (EPI) in Senegal. In addition, 55.12% had received the typhus vaccine and 30.24% the pneumococcal vaccine. Furthermore, 35.12% of the children had received oral penicillin prophylaxis, and 38.54% had received malaria prophylaxis. Fever was the most frequent symptom, observed in 76.73% of patients. The majority of infections were Ear, Nose, and Throat (ENT) infections (35.35%). Bacterial infection was the most common (74.64%), and the most frequent pathogens were *Streptococcus pneumoniae* (3), *Escherichia coli* (3), and *Mycobacterium tuberculosis* (2). First-line antibiotic therapy was administered to 91.2% of patients, and the outcome was favorable in 83.57%. **Conclusion**: In our study, bacterial ENT and respiratory infections were more frequent. Children aged 5 to 10 years were more affected, and *Streptococcus pneumoniae* was the most frequent pathogen. Hence the importance of oral penicillin antibiotic prophylaxis and pneumococcal vaccination.

Keywords

Sickle Cell Disease, Infections, Pneumococcus, Children

1. Introduction

In children with sickle cell disease, infections are among the most serious acute complications. They are a major cause of mortality if not managed appropriately [1]. Indeed, the risk of infection is particularly high in children due to functional asplenia, organ dysfunction, and other factors [2]. This susceptibility to infections is more common in African contexts, characterized by significant socioeconomic and health challenges, limited access to healthcare, a high prevalence of endemic infectious diseases, and precarious living conditions [3]-[5]. It is in this context that we conducted this study. Our objective was to investigate the infection profile in children with major sickle cell syndromes followed at USAD. More specifically, the aim was to describe the sociodemographic and epidemiological aspects, to analyze the clinical, paraclinical and evolutionary aspects of these infections, to identify the pathogens involved, and to investigate the associated factors.

2. Patients and Methods

We conducted a descriptive and analytical cross-sectional study from January 2nd to December 31st, 2023, among children followed for major sickle cell syndromes in the Outpatient Unit for Children and Adolescents with Sickle Cell Disease (USAD) in Albert Royer National Children's Hospital (CHNEAR) in Dakar. We included children under 16 years of age who were regularly followed in the USAD and who had experienced at least one infectious episode during 2023. We excluded children with incomplete or unavailable records, or with undocumented infections. Recurent infections was defined by at least 2 infections in the same patient. Socio-demographic data, sickle cell disease characteristics, preventive measures, medical history and infectious episodes in 2023 were collected on a survey form and analyzed using R software version 4.4.1 and Excel Professional Plus 2021. For the analytical study, we used Pearson's Chi-squared test with a significance level of 5%.

3. Results

Of the 4654 consultations performed in 2023 at the USAD, 1785 were emergencies, including 508 for infections. These infections represented 10.92% of all consultations and 28.46% of emergencies. However, according to our inclusion criteria, our sample consisted of 205 patients or consultants (n) who experienced a total of 280 infectious episodes or consultations (N). Males were slightly predominant (53.65%), with a sex ratio of 1.15. The mean age of the children was 109.88 ± 108 months, with a median of 48.12 months and a range of 13 to 192 months. Among them, 41.87% were between 5 and 10 years old (Figure 1).

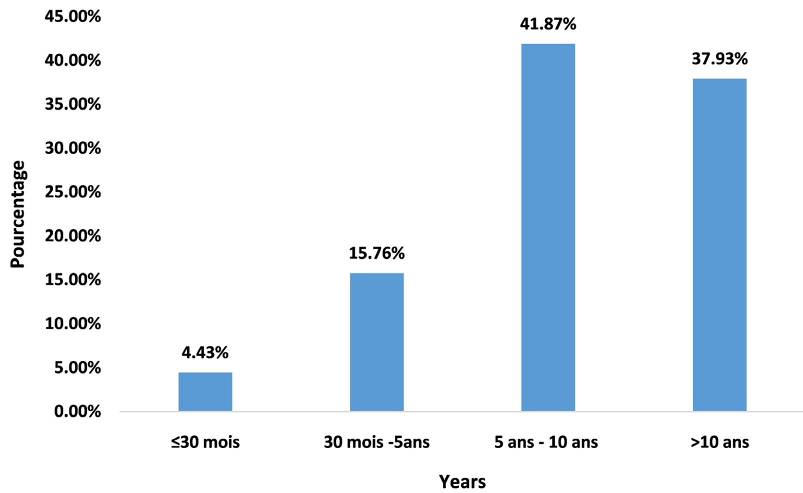

Figure 1. Age distribution of patients.

The majority of patients came from Dakar and its surrounding area (79.51%). The fathers were predominantly self-employed (72.27%). The homozygous SS form was predominant (93.63%). The mean baseline hemoglobin level was 7.84 g/dl, with a median of 8 and a range of 6 to 11.5. Infection was the second most common symptom of sickle cell disease (24.35%; n = 47) after pain (43.01%; n = 83). Vaccination was up-to-date in the Expanded Program on Immunization (EPI) of Senegal for 90.73% of children (n = 186). Regarding recommended vaccines, 55.12% of children had received the typhoid vaccine (n = 113), and 30.24% the pneumococcal vaccine (n = 62). Oral penicillin prophylaxis was observed in 72 patients (35.12%) and malaria prophylaxis in 79 patients (38.54%). A history of infection was found in 175 patients (85.37%), primarily bacterial infections (87.43%; n = 153). A total of165 patients (80.49%) had already experienced acute complications of sickle cell disease, and 25 patients (12.19%) already had chronic complications. Hydroxyurea was prescribed in 16 patients (7.80%). Clinically, fever was the most frequent symptom (76.73%, n = 211). Ear, Nose, and Throat (ENT) infections (35.35%; n = 99) and respiratory infections (32.85%; n = 92) were the most frequent. Biologically, CRP was measured during 264 infectious episodes (94.3%) and was positive in 242 cases (91.67%). Leukocytosis was observed in all patients, with a mean white blood cell count of 19,590 ± 7.30/mm^3. (Table 1).

Table 1. Complete blood count results.

	Mean ± ET	Median	Extremes
Leucocytes (mm^3)	19.59 ± 7.30	18.70	[3.63 - 53.73]
Neutrophiles (mm^3)	12.44 ± 6.18	11.78	[1.07 - 41.80]
Red cells	2.80 ± 0.90	2.68	[0.69 - 4.21]
Reticulocytes (mm^3)	309496.45 ± 128921.72	326126.00	[56700 - 647000]
Hemoglobine (g/dl)	7.63 ± 1.38	7.7	[2.2 - 11.4]
MCV (fl)	83.51 ± 8.29	83.3	[61 - 112.6]
MCH (pg)	28.20 ± 3.31	28	[19.3 - 38.8]
Platelets (mm^3)	418.10 ± 157.33	405	[64 - 980]

A bacterial origin was confirmed in 74.64% of cases (n = 209) (Table 2).

Table 2. Causes of infection (n = 280).

Cause of infection	Absolute frequency (n)	Relative frequency (%)
Bacterial	209	74.64
Viral	57	20.35
Parasitic	11	3.92
Fungal	3	1.07

The most frequently prescribed microbiological tests were the Rapid Diagnostic Test (RDT) for malaria (26.43%) with a positivity rate of 2.7%, thick blood smear (13.93%) with a positivity rate of 5.12%, and blood culture (5%), which was positive in 35% of cases (Table 3).

Table 3. Pathogens and sample sources.

Microbiology	**Absolute frequency (n)**	**Relative frequency (%)**
Blood culture	14	5
Positive	5	35
Streptococcus pneumoniae	2	
Salmonella spp.	1	
Staphylococcus aureus	1	
Staphylococcus spp.	1	
Urine culture	7	2.5
Positive	4	57
Esherichia coli	3	
Bacille gram neg	1	

Continued

Expectoration culture	3	1.07
Positive	2	66.6
Mycobacterium tuberculosis	1	
Streptococcus p decapité	1	
Coproculture	4	1.43
Parasitological stool examination	6	2.14
Positive	1	16.6
Kystes *Entamoeba coli*	1	
Malaria rapid diagnosis test	74	26.43
Positive	2	2.7
Thick drop	39	13.93
Positive	2	5.12
Tuberculin intra dermo reaction	3	1.07
Gene Xpert	10	3.57
Positive	2	20
AgHbS	2	0.71
Ac anti VHC	1	0.36
Positive	1	

The most common pathogens were *Streptococcus pneumoniae* (3), *Escherichia coli* (3), and *Mycobacterium tuberculosis* (2). A significant relationship was observed between the occurrence of recurrent infections and non-compliance with preventive anti-infective measures:

- Pneumococcal vaccination (p = 0.004; OR [95% CI] = 3.49 [1.48-8.3]).
- Meningococcal vaccination (p = 0.006; OR [95% CI] = 2.67 [1.36-5.23])
- Oral antibiotic prophylaxis (p = 0.008; OR [95% CI] = 2.86 [1.33-6.13])

Any relationship was found between infection, genetic profile or sickle cell severity. Hospitalization was indicated in 255 cases (91.2%), mainly for bacterial infections. A first-line antibiotic therapy, based on third-generation cephalosporins, was administered to 91.2% of patients (n = 255). In 5.49% of cases (n = 14), the antibiotic was adjusted after an antibiogram. An artesunate-based antimalarial was prescribed to 2 patients (0.71%), and 3 patients (1.07%) received imidazole-based antifungals. Deworming was prescribed in 21 cases (7.5%). Other symptomatic treatments were used as indicated (intravenous fluids, electrolytes, analgesics, antipyretics). The outcome was favorable in 83.57% of cases (n = 234). Complications were observed in 16.43% of patients (n = 46), and sequelae in 1.9% of cases (n = 5).

4. Discussion

The frequency of infectious emergencies found in our study (28.46%) was close to that of Mabiala in Brazzaville, Congo (36.6%) [6]. This confirms the recurrence of infections in children with major sickle cell syndromes, related to their increased susceptibility to bacterial infections [7]. Indeed, this frequency has decreased significantly over time. In 1997, it was 56% in this same cohort, according to Diagne *et al.* [4]. Later, in 2017, 20 years after the study by Diagne *et al.*, this frequency had fallen to 33.96% in the same hospital [8]. This decrease in the frequency of infections could be explained by an improvement in the quality of care for the disease in recent years. Indeed, the opening of the USAD has contributed to the training of human resources, to raising awareness among parents during therapeutic education sessions for better application of preventive measures, particularly against infections.

The slight male predominance observed in our study (male/female sex ratio = 1.15) was also reported in other studies. Diagne *et al.* found a sex ratio of 1.08, Tambo *et al.* a sex ratio of 1.2, while Yé Diarra *et al.* found 1.44 [9]-[11]. These results confirm the trend observed in our study. Gbadoé *et al.* and Thuilliez *et al.* observed a sex ratio of 1 [12] [13]. Nacoulma *et al.* in Bobo Dioulasso, for their part, found a female predominance, with a sex ratio of 0.8 [14]. The variability of these different results is explained by the fact that neither sickle cell disease nor susceptibility to infections is influenced by sex. Indeed, a study conducted in Saint-Louis, Senegal, highlighted regional disparities in the management of sickle cell disease [15]. This situation was confirmed during the COVID-19 pandemic, during which sickle cell disease was considered as a risk factor, despite the absence of any particular susceptibility to viral infections [16]. In our patients, the mean age at the time of the study was 109.88 months (±108 months), with a predominance of the 5 - 10 year age group. This distribution was comparable to data in the literature, which showed a high frequency of infectious complications at this age [8]. Indeed, school-aged children are the most exposed to these pathogens in the school environment. In 2019, a WHO report also corroborated these observations, highlighting the increased vulnerability of children with sickle cell disease to infections at this age [17]. In 2015, in the study of the first pilot program for neonatal screening for sickle cell disease in Saint Louis, Senegal, Diop *et al.* found that the first clinical signs of sickle cell disease generally appeared between 6 and 12 months [18]. This is comparable to the median age in our study, which was 12 months. Tshilolo *et al.* reported a result around 18 months, with extremes from 3 months to 120 months [19].

As for the mean age at diagnosis, it was 34.22 ± 29.21 months in our study and 30 months in Burkina Faso in 2017 [1]. This confirms the significant diagnostic delay in countries without national newborn screening programs. In Ghana and Nigeria, where newborn screening programs exist, the ages at diagnosis are earlier (<6 months), which considerably reduces the risk of complications. Indeed, the WHO recommends early screening for sickle cell disease at birth to allow for rapid and appropriate care for children [20]. The mean age at the start of follow-up for our patients was 44.52 months, which is comparable to the results of Ndiaye *et al.* [21] in 2016, who found a mean of around 40 months. Indeed, in sub-Saharan

Africa, specialized medical follow-up is generally delayed, after serious manifestations such as vaso-occlusive crises or severe infections [22].

The SS genotype was predominant (93.63%) in our study, confirming the high prevalence of this form in Senegal and some other countries in the sub-region [22]. Clinically, pain was the most frequent presenting symptom (43.01%). In fact, vaso-occlusive crisis is universally recognized as the most frequent clinical manifestation of sickle cell disease [23]. Furthermore, the majority of children (nearly 75%) had experienced between 3 and more than 5 infectious episodes since the start of their follow-up. This reflects a high prevalence of recurrent infections, particularly among patients with poor adherence to prophylactic measures. Moreover, vaccination coverage was satisfactory in the Expanded Program on Immunization (EPI), with 90.73% coverage. This was not the case for the recommended complementary vaccines, for which coverage was insufficient, particularly for the pneumococcal vaccine (30.24%). According to WHO regional reports, the low vaccination coverage in West Africa in 2022 was due to a lack of awareness and limited access to vaccines, exacerbated by the COVID-19 pandemic. The low use of antibiotic prophylaxis (35.12%) could also be explained by the unavailability of Oracilline in Senegal for several years. The low coverage rate for malaria prophylaxis (38.54%) could be explained by the trivialization of malaria in Senegal, despite its significant morbidity and mortality. Regarding infections, the origin was primarily bacterial (74.64%), and the location was mainly ENT (35.35%) and respiratory (32.85%). Moreover, our results were similar to those of regional studies that had identified *Streptococcus pneumoniae* as a major pathogen in children with sickle cell disease, due to increased susceptibility linked in part to functional asplenia [5] [7] [24].

In Senegal, vaccination against encapsulate organisms is prescribed to children but must be supported by families. Pneumococcal vaccination is included in national programm of immunization for all children.

Clinically, fever was the earliest sign of infection (76.73%), reported by Aygun and Odame as the main symptom during severe infectious episodes, particularly those caused by *Streptococcus pneumoniae* or Haemophilus influenzae [22]. Indeed, in 2015 in Tanzania, 80% of infectious episodes were associated with fever, according to Makani *et al.* [25]. The other signs were primarily respiratory. According to Tshilolo *et al.*, these symptoms were often associated with pneumonia or acute chest syndrome, one of the most serious complications of sickle cell disease [19]. Laboratory findings showed leukocytosis in all patients, which is typical in sickle cell disease, even in the absence of any infectious process. However, in the presence of a clinical infectious syndrome, a white blood cell count above 20,000 leukocytes/mm^3 strongly suggests infection [26]. The mean hemoglobin (Hb) level was 7.63 ± 1.38 g/dL, comparable to that reported by Okuonghae *et al.*, who also reported similar levels (7 - 8 g/dL) [27]. CRP was measured in 264 infectious episodes (94.3%) and was positive in 242 cases (91.67%). Tshilolo *et al.* reported similar results of elevated CRP in severe infectious episodes. This confirms that CRP is a reliable indicator of bacterial infection in individuals with sickle cell disease [19]. The pathogens isolated in our study were comparable to those reported in the literature. Indeed, in Bamako, Diakité *et al.* identified similar pathogens, including *Streptococcus pneumoniae* (4 cases) and Salmonella enterica serotype Typhi (4 cases), in blood cultures [5]. This small difference could be explained by better vaccination coverage in our study. In Burkina Faso, Douamba *et al.* also confirmed the predominance of *Escherichia coli* in urinary tract infections [1]. The factors significantly associated with infections were the absence of preventive anti-infective measures (vaccination, antibiotic prophylaxis). Indeed, these measures have proven effective, but their implementation is often limited by families' lack of financial resources and the absence of subsidies from health authorities. In terms of treatment, first-line antibiotic therapy was initiated in 91.2% of cases, primarily with cephalosporins (29.80%) and penicillins (24.71%).

Because of the local pathogens specifities antibiotic therapy should be adaptated to the context. Other treatments were based on hydration (97.86%), to reduce blood viscosity, improve microvascular flow, and prevent complications related to dehydration [28]. A blood transfusion was performed in 24.29% of patients, a result comparable to that of Diagne *et al.*, who reported 22% of transfusions in cases of severe complications. Deworming was prescribed for 21 patients (7.5%). As a reminder, intestinal parasitic infections can worsen anemia and reduce patients' immune capacity. Furthermore, Koffi *et al.* emphasized the importance of screening for and treating parasitic infections in children with sickle cell disease in Côte d'Ivoire [29]. Three patients (1.07%) received antifungals, even though fungal infections are often observed in immunocompromised patients or after prolonged antibiotic therapy. In Tanzania, isolated cases of opportunistic fungal infections were reported by Makani *et al.* in sickle cell patients with severe immunosuppression [30].

Antimalarial drugs, prescribed to 0.71% of patients, represented a low proportion in this study, likely due to the malaria prophylaxis implemented. However, in areas of high endemicity, malaria remains a frequent cause of morbidity and mortality in sickle cell patients [31]. Indeed, its frequency was 0.5% in this same cohort in 2022 [32]. The infection's course was generally favorable in 83.57% of cases. However, complications were observed in 16.43% and sequelae in 1.9%, such as limping due to unequal limb length.

Study limitations: The main limitations of this study are retrospective type, the single-center design, in an outpatient referral unit and the difficulties to have microbiology confirmation. Antimicrobial resistance was not studied.

5. Conclusions

This study's results show the frequency of infections in children with sickle cell disease. Hence, the importance of prophylaxis by immunization, penicillin therapy, malaria prophylaxis.

Children with sickle cell disease are a high-risk population for bacterial infections.

A public health prevention strategy should be implemented to reduce infection risque in sickle cell disease. Awareness and advocacy are very important to improve families adherence to prophylaxis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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