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Infection and Impact of Prophylaxis in Sickle Cell Children: A Cross-Sectional Study of 327 Sickle Cell Children Admitted in Emergency Department of Albert Royer Children Hospital in Dakar, Senegal

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Abstract

Background: Pneumococcus has been identified in several studies as the infectious agent most frequently found in children with sickle cell disease. However, some studies note an emergence of other infectious agents, especially in sub-Saharan Africa. Prophylactic measures, mainly targeting pneumococcus, our study aimed to describe the epidemiological, clinical and biological aspects of infections in children with sickle cell disease and to measure the impact of prophylactic anti-infectious measures. **Methods:** We conducted a cross-sectional study over a 5-month period from January 2022 to May 2022 in children and adolescents with sickle cell disease admitted to the emergency department of Albert Royer Children's Hospital. Epidemiological, clinical, biological and therapeutic data were collected by Excel and used by SPSS 28.0 software. **Results:** of the 327 patients seen in the emergency room, 107 (32.7%) were admitted for infection. Pulmonary infection was the most common, with 46 patients (42%), followed by bone infections. Of the 46 blood cultures performed during this period, only one came back positive for pneumococcus. All patients initially received probabilistic antibiotic therapy. Vaccination coverage against pneumococcus was 19.26% in these patients. 60% of children under 5 were on antibiotic prophylaxis. There was a statistically significant association between the absence of vaccination coverage and the occurrence of infection. **Conclusion:** Infections account for around a third of emergency room admissions for children with

sickle cell disease, and are dominated by respiratory and osteoarticular infections. Despite this, coverage of prophylactic measures such as vaccination and antibiotic prophylaxis remains low, due to their cost.

Keywords

Infection, Sickle Cell Anemia, Children, Prophylaxis

1. Introduction

Sickle cell anemia (SCA) is the world's most common genetic disease, affecting more than 300,000 newborns every year [1] [2]. Infections are the main cause of morbidity and mortality in children with sickle cell disease, particularly before the age of 5 [1]-[4]. They are mostly bacterial, but can also be viral; or parasitic, notably malaria infection in malaria-endemic areas such as Senegal.

In high income countries, mortality among sickle-cell-affected children has fallen considerably, approaching that of non-sickle-cell-affected children, thanks to preventive measures, notably against pneumococcal disease. In Africa, although a drop in infant mortality has been noted over the last decade, infection remains the main cause of mortality in sickle-cell children under 5 years of age. This difference is linked, on the one hand, to the cost and health system difference: in 2017, essential care coverage was highest in Europe, North America and East Asia (77% in the three zones) and lowest in South Asia (53%) and sub-Saharan Africa (42%) and for Senegal, between 2004 and 2009, direct payments by households represented 37% and over 50% of current healthcare expenditure [5]. On the other hand, by the different bacterial ecology between developed and sub-Saharan African countries [1] [6].

In 2015, the study conducted by Boiro *et al*. on 138 patients in Senegal found a proportion of infections of 54.6% despite 74.8% of these patients being on antibiotic prophylaxis [7]. In 2017, again in Senegal, Deme *et al*. found a 35% proportion of infections in children and adolescents with sickle cell disease in a sample of 163 patients, with one germ isolated: Citrobacter Freundii [8]. In Nigeria in 2018, Bello and al characterized the germs isolated from sickle cell children and found 39% Salmonella Typhi infection, followed by Streptococcus pneumoniae at 14.7%, then Salmonella para typhi and Staphylococcus aureus at 5.8%. In this study, gram-negative bacteria accounted for over 50% of infections such as in studies conducted in African countries [6] [9]-[12].

Our study aimed to characterize infections in children with sickle cell disease and to assess the influence of preventive anti-infectious measures in these patients.

2. Methods

2.1. Study Design

Cross-sectional study covering the period from January 1, 2022 to May 31, 2022.

Patients with an established diagnosis of sickle cell anemia, received in the emergency department, aged 0 to 21 years.

2.2. Study Setting

Our study was carried out at Albert Royer Children's Hospital in the emergency department and in the emergency sector of the outpatient unit for sickle-cell adolescents and children at the same hospital. Albert Royer Children's Hospital is a pioneering site in the care of children with sickle cell disease in Senegal, with an active file of about 4,000 patients.

Definitions and thresholds values; Infection was considered when:

- Isolation of a germ from a microbiological sample (proven infection);
- Presence of fever > 38.5˚C and/or infection strongly suspected by clinical signs associated with a marked biological inflammatory syndrome (CRP >40, and/or hyperleukocytosis > 16,000/mm^3).

2.3. Data Collection

Data sources were patient's physical medical records and data collected were recorded on an excel file.

2.4. Data Analysis

Data were analyzed using Excel and SPSS 28.0. A statistically significant association was defined by a p. value < 0.05.

3. Results

A total of 332 files were studied. Excluding incomplete files and patients above 21 years, there were 327 files.

Of the 327 sickle cell patients seen in emergency departments, 107 (32.7%) were admitted for infection. The median age of the cohort was 9 years. The extremes were 7 months and 21 years. There was a predominance of males, with a sex ratio of 1.18.

3.1. Previous Follow-Up

Of these patients, 96.3% (315 patients) had follow-up for sickle cell disease, while the remaining 12 (3.7%) had no regular follow-up, or failed to keep follow-up appointments. Among patients admitted for infection, 98 out of 107 (91.5%) had regular follow-up.

All type of sickle cell disease (SCD) were represented, with homozygote predominating at 94.5% (309 patients), followed by SC sickle children, 14 patients (4.28%) and 4 Sβ thalassemia (1.22%). For infected patients, 99% were SS (106 patients) and only one was SC.

Median baseline hemoglobin was 8 g/dl, with extremes of 6 and 12 g/dl. 6 of the 327 patients (1.84%) were on hydroxyurea and 2 on transfusion therapy (0.6%).

Comorbidities found in these patients was dominated by asthma 13 patients

(3.97%), then heart disease, 2 patients (0.62%) and other such as hypothyroidism, lupus and nephrotic syndrome. Asthma was the only comorbidity found in the proportion of infected sickle cell patients (5 patients or 4.6%).

Coverage of mandatory vaccines (from 0 to 15 months) was 93.88% (307 patients) among sickle-cell patients admitted to the emergency department. This coverage was higher for infected patients: 97% (104 patients).

The following graphs (Figure 1) illustrate coverage of specific vaccines to sickle cell disease follow-up in particular pneumococcal polysaccharide vaccine, anti-typhoid vaccine and meningococcal vaccine.

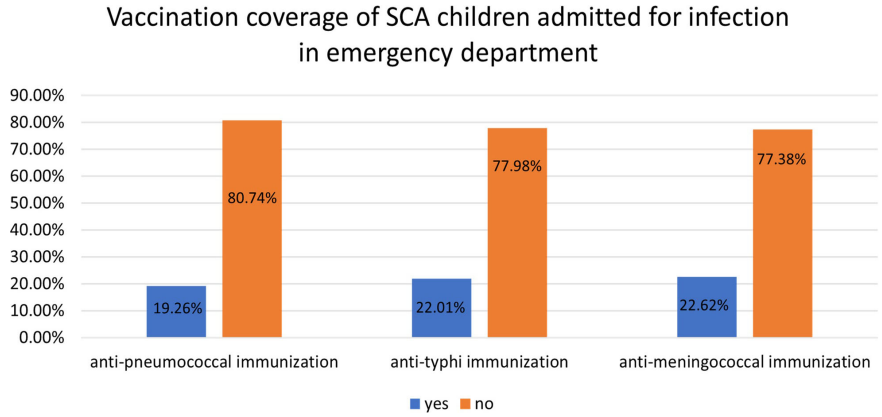

Figure 1. Vaccination coverage of SCA children admitted for infection in emergency department.

43 patients (13.15%) were on antibiotic prophylaxis. In the 0 to 5 age group, 42 patients (60% of cases) were under antibiotic prophylaxis. In the infected sickle cell group, 15 patients (14%) were under antibiotic prophylaxis. This antibiotic prophylaxis was based on penicillin V for all patients. No patient was on malaria prophylaxis during the study period.

The number of patients who were both correctly vaccinated and on antibiotic prophylaxis was 39 (11.93%).

3.2. Clinical Presentation

The main reason for consultation in the emergency department was pain 251 patients (76%), followed by fever 107 patients (32.7%) and asthenia 25 patients (7.6%).

For patients admitted at emergency department, vaso occlusive crisis (VOC) was the main diagnostic different diagnoses of patients admitted to the emergency department during the study period.

3.3. Clinical Signs

The most common clinical signs in patients admitted to the emergency department were fever above 38.5˚C, clinical anemia (pallor), auscultatory abnormality and respiratory distress. Hypoxia and bone swelling were present in less than 5%

of cases. Four patients were malnourished.

3.4. Type of Infection

Several types of infection were identified. The main site of infection was pulmonary (46 patients or 42%), comprising 42 cases of ACS, 3 cases of purulent pleurisy and one case of pulmonary tuberculosis. Pulmonary infections were followed by osteoarticular infections, with 5 cases of septic arthritis and 6 of osteomyelitis. There were as many digestive infections (gastroenteritis) as ENT infections (7 cases or 6.4%). ENT infections were all tonsillitis. 2 cases of transient erythroblastopenia were recorded based on severe anemia with low reticulocytes level. 2 patients presented with sepsis, one of which was complicated by septic shock leading to death. Malaria was found in 4 patients, with no signs of severity according to the WHO.

The median white blood cell count was 12,700/mm^3 in patients admitted to the emergency department, and the median CRP level was 45.54 mg/l in the proportion of infected patients, with a maximum of 289.2 mg/l.

3.5. Microbiological Samples

A total of 137 samples were taken from these patients. Bacteriological samples accounted for 54.7% (75 samples), including 46 blood cultures, 11 osteoarticular punctures, 3 pleural punctures, 1 lumbar puncture, 3 ECBU and 11 sputum PCRs for Mycobacterium tuberculosis. No viral samples were taken. Thick-film tests for plasmodium were carried out in 62 patients. The positivity rate for these samples was 4.3%. This corresponded to 5.6% of infected patients with an isolated germ.

3.6. Identification of Germs

6 cases of microbiologically documented infections. These were one case of Pneumococcal sepsis isolated by blood culture, one case of pulmonary tuberculosis isolated by PCR on sputum and 4 cases of malaria isolated by thick blood smear. No biological fluid puncture was used to isolate a germ.

3.7. Contribution of Imaging

Imaging made a considerable contribution to the diagnosis of infections, especially osteoarticular, pulmonary and soft-tissue infections. A total of 99 imaging examinations were carried out, including 59 chest X-rays with parenchymal infiltrates in 43 cases and 3 cases of pleural involvement. Ultrasound scans of the limbs were carried out in 8 patients, 5 of whom showed images of subperiosteal abscesses compatible with the diagnosis of osteomyelitis. 12 joint ultrasound scans were performed, 5 of which revealed a collection compatible with septic arthritis. All soft-tissue ultrasound scans revealed abscesses.

3.8. Antibiotic Treatment

All patients (107 patients) admitted for infection received probabilistic antibiotic

therapy. 3rd generation cephalosporins were the molecules most frequently used 105 patients (98.1%) in infected patients. Followed by erythromycin, 42 patients (12.84%); aminoglycosides, 19 patients (5.7%) then ciprofloxacin, 8 patients (2.45%). Amoxicillin was used in 5 patients (1.53%) and vancomycin in one (0.31%). One patient received anti-tuberculosis treatment based on Rifampicin, Isoniazid, Ethambutol and Pyrazinamide.

3.9. Anti-Malarial Treatment

The 4 patients with malaria infection and a positive thick smear without signs of severity according to WHO, received artesunate for the management of their malaria attacks.

3.10. Evolution

Clinical improvement in 99% of cases, with no more fever and normalization of CRP. 1 case of death was recorded in the infected group: a 3-year-old female infant. 7 patients were taking hydroxyurea after hospitalization in the emergency department, including 2 in the infected group.

3.11. Impact of Prevention

Quality of follow-up and infection

There was a statistically significant association ($p < 0.005$) between the quality of follow-up and the occurrence of infection (Table 1). Infected patients had less regular follow-up of their disease than the non-infected group (Chi-square test).

Table 1. Impact of follow-up in infection occurrence.

			Infection		Total
			No	Yes	
Follow-up	Non-regular	Number	3	9	12
		Percentage	25.0%	75.0%	100.0%
	Regular	Number	217	98	315
		Percentage	68.9%	31.1%	100.0%
Total regular and non-regular		Number	220	107	327
		Percentage	67.3%	32.7%	100.0%

**Khi-deux Pearson's test* = 0.003.

Preventive measures

There was a statistically significant association between sickle-cell-specific supplementary vaccines and the occurrence of infection. This association was not found for penicillin V antibiotic prophylaxis. Table 2 shows these different associations.

Table 2. Relation between preventive measures and infection.

Preventive measures	Infected	Non-infected	p. value
anti-pneumococcal immunization	11 (17.5%)	52(82.5%)	**0.0001**

Continued

anti-meningococcal immunization	14 (18.9%)	60 (81.1%)	**0.0001**
anti-typhic immunization	13 (18.1%)	59(81.9%)	**0.0001**
Antibioprophylaxis by penicillin V	15 (34.9%)	28 (65.1%)	0.746
Total	107	220	

4. Discussion

Sickle cell disease is the most widespread genetic disorder in the world [13] [14]. Infections are the main cause of mortality in children with sickle cell disease, especially in sub-Saharan Africa, and infection should be suspected when children with SCD present any fever (typically defined as 38.5˚C or higher) [15]. The results of this study show that infections in sickle-cell patients are a frequent cause of admission to emergency departments, with a frequency of 32.7%. This proportion tends to decrease when compared with studies by Boiro *et al*., Thiam *et al*., or Dème *et al*. on similar populations [7] [8] [16]. The median age in our study was 9 which is close to the mean age of sickle-cell children with a positive blood culture in Yee M.D.'s study (7.5 years) [17].

4.1. Type of Infection

The main types of infection found were respiratory infections followed by osteoarticular, then digestive infections. This was superposable with the results of Thiam *et al*., in 2018 in Senegal. Because of their pathophysiology, we considered ACS to be infections. Moreover, the difficulty of identifying a germ in both pulmonary infections and ACS makes the distinction uncertain [18]. There was a significant proportion of highly suspected infections with fever but without bacteriological evidence (20.3%). This last category remains an indication for the initiation of broad-spectrum probabilistic antibiotic therapy recommended on the basis of several descriptive studies and expert opinion [12] [19] [20]. In our study, all these patients received antibiotic therapy, with an improvement in their biological inflammatory syndrome under antibiotic treatment.

4.2. Germ Identification

Our study identified only one germ out of 46 blood cultures taken. There are few studies on the characterization of germs responsible for infections in sickle-cell patients in Africa [1]. The study by Bello *et al*. in Nigeria identified 39% Salmonella typhi infections, followed by Streptococcus pneumoniae at 14.7%, Salmonella para typhi and Staphylococcus aureus at 5.8%. In this study Gram negative bacteria remain higher than infection by Streptococcus Pneumoniae, this contrast with the most common pathogens found in higher income countries as the study by Yee ME *et al*. was Streptococcus pneumoniae 16%, followed by Staphylococcus and Streptococcus (*viridans* group and *pyogens)*, Salmonella species at 6.4% [9] [17]. Several studies have shown a low positivity threshold for blood cultures, such as the study by B. S. Shihabuddin and C.A. Scarf, where out of 307 blood cultures, only 1 came back truly positive and 6 were contaminations [20]. A limitation of

our study is the lack of information on antibiotic use prior to admission to the emergency department. In fact, the use of antibiotics could explain the low positivity of bacteriological samples. During the period of the study, viral tests have not been performed, which limits our understanding of the role of these viral infections in this study.

4.3. Antibiotic Treatment

Due to the low positivity of blood cultures, empirical antibiotic therapy was initiated with 3rd generation cephalosporins in 98.1% of cases. This practice is in line with international recommendations, considering the functional asplenia and the high risk of sepsis in this condition [12].

4.4. Preventive Measure

Penicillin prophylaxis was effective in under-5 years in 60% of cases. We found no association between this antibiotic prophylaxis and the absence of infection. Several studies have demonstrated the benefits of oral antibiotic prophylaxis with penicillin [4] [21]. However, this practice is not uniform in sub-Saharan Africa, with the study by Coria AL. *et al*. showing that 29% of practitioners did not prescribe antibiotic prophylaxis for their sickle cell patients [12]. In Studies conducted in Ghana, Tanzania and Nigeria; prescription of penicillin prophylaxis was effective in 7%, 10% and 17,2% respectively for sickle cell children [10] [22]-[24]. This was due to the irregular availability of the syrup form of penicillin V in Senegal, but also to the cost, as this treatment is not reimbursed. In addition, the infrequent isolation of Streptococcus pneumonia from febrile SCA children in sub-Saharan Africa could underlie this practice [6] [9] [25]. And finally, studies show a low adherence to penicillin V prophylaxis [26] [27].

Malaria prophylaxis was not carried out in any of the patients included in this period of the study. This prophylaxis was systematic in the study by Coria *et al*. In Senegal, anti-malarial prophylaxis based on monthly doses of Sulfadoxin Pyrimethamin is recommended from June to October, corresponding to the peak malaria epidemic. However, the occurence of 4 malaria infections could suggest adopting year-round prophylaxis, as in other African countries [28].

Immunization coverage was low (below 30%) for all specific sickle cell vaccines, such as meningococcal, anti-typhoid and pneumococcal. 20 years earlier Diagne I *et al*. show similar coverage for pneumococcal immunization and we note a slight improvement in anti-typhoid immunization 22% VS 8,4% in 2000 for similar population [29]. Better results were found in Brazil, notably for Pneumococcal vaccine PPSV23: 61% for the first dose [30] However, all these studies highlight under-vaccination rate in this selected high-risk group. This, could be linked to the cost of these vaccines, which are not reimbursed, as well as to their irregular availability. Subvention for sickle cell children by government should be offered by government.

5. Conclusion

Infection is a frequent cause of admission to the emergency department for SCA

children, requiring broad-spectrum antibiotic therapy. The main germs found in sickle-cell patients are encapsulated germs, although these can be difficult to detect. Infection can lead to death, especially in children under 5. To counter this, a number of preventive measures have been established and have led to a marked improvement in the survival of children with sickle cell disease in northern countries. These measures remain difficult to access in Sub-Saharan Africa, and explain the low coverage of these preventive measures in this region. In addition, several studies have highlighted the emergence of other pathogens such as enterococcus which are not targeted by these prophylaxes. However, further multicentric studies are needed to better describe the epidemiology of isolated germs during infection of SCA children.

Ethical Considerations

The medical data was collected following informed consent from the parents of the study participants.

Authors' Contributions

Specify the contribution to the work and write-up of the manuscript for each person listed as author.

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Corrections: Awa Kane, Indou Dème, Aliou Thiongane, Papa Moctar Faye, Amadou Lamine Fall, Ousmane Ndiaye.

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Conflicts of Interest

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

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