Severe Bacterial and *Plasmodium Falciparum* Infections in Febrile Children with Sickle Cell Disease Receiving Organized Specialty Care in a Referral Center in Sub-Saharan Africa: lessons for Clinical Practice

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Abstract: The burden of severe bacterial and malaria infections in children with SCD has been reduced through the use of prophylactic antibiotics and chemoprevention with *Sulfadoxine-pyrimethamine.* However, such therapies have the potential to promote bacterial and parasitic resistance. To our knowledge, no study has been conducted to determine whether systematic use of prophylactic antimicrobials in children with SCD has an impact on resistance patterns in sub-Saharan Africa. The aim of our study was to determine the incidence and the outcome of severe bacterial and *P. falciparum* infections in this context. 231 children with SCD and new onset fever associated with either acute pneumonia, urinary tract infection, cholecystitis, meningitis, acute osteomyelitis, or *P. falciparum* infections were entered into the study. The children in the cohort were an average age of 93 months (± 44 months) and were all followed in a referral center in Western Africa. The 231 children represented 36.67% of the patients regularly followed in the center during the study period and included 183 SS, 26 SC, 12 Sβ°thal, 10 Sβ$^+$thal. There were 144 boys and 87 girls in the cohort. The incidence of severe bacterial and *Plasmodium falciparum* infections were lower than those reported in the general pediatric or sickle cell population in the absence of regular follow-up (ie 5.2, 1.4, 1.0 and, 4.1 *per* 1000 person/month for urinary tract infections, acute pneumonia, bacteremia and *P. falciparum* malaria respectively). We observed bacterial strains to be mainly in the *Enterobacteria* family with high levels of antibiotic resistance. No cases of *Streptococcus pneumoniae* bacteremia were found. *Sulfadoxine-pyrimethamine* resistance was observed at high levels. In light of these findings, prophylactic antibiotherapy and antimalarial chemoprevention guidelines in sickle-cell children should be revisited in the context of organized SCD care in sub-Saharan Africa.

Keywords: Febrile, *P. falciparum,* Infection, Prophylactic antibiotics, Severe bacterial, Sickle cell disease, Standardized care, Sub-Saharan Africa.

INTRODUCTION

Sickle cell disease is the most common structural hemoglobinopathy. The number of births of sickle cell affected newborns worldwide is estimated to reach 405,000/year in 2050, with the majority of these births (75%) in sub-Saharan Africa and India [1]. In the natural history of sickle cell disease, infection is one of the main causes of childhood mortality and is also a trigger for severe complications with a poor prognosis [2, 3]. In malaria endemic areas, the most common agents involved in the occurrence of these infectious complications include encapsulated bacteria including *Streptococcus pneumoniae* and parasites including *Plasmodium falciparum* (*P. falciparum*) [4-7]. Reducing the incidence of these infections improves survival of SCD patients [2, 8-10]. Thus, guidelines for management of fever in children with SCD recommend systematic use of empiric antibiotics with coverage against encapsulated organisms along with a blood culture and a rapid laboratory test for malaria [11, 12]. However, the use of prophylactic antimicrobial therapy carries a potential risk of the development of bacterial or parasitic resistance to prescribed agents [13, 14]. Our study specifically looks at the use of empiric antimicrobial therapy in the context of severe infections in children receiving specialized care for SCD in sub-Saharan Africa. Our aims were to *i)* evaluate the incidence of severe bacterial and *P. falciparum* infections and to analyze the sensitivity profile of these isolated organisms, *ii)* to evaluate the incidence of sulfadoxine/pyrethamine resistance in a cohort of febrile sickle cell children followed in a referral center in sub-Saharan Africa.

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PATIENTS AND METHODS

From April 2014 to January 2016, we prospectively reviewed all cases of children with SCD, aged 6 months to 15 years, who presented with fever (body temperature ≥ 38 ° C) to the "Centre de Recherche et de Lutte contre la Drépanocytose (CRLD)", a referral facility for the management of individuals affected by SCD in Bamako, Mali. The preventive follow-up of children with SCD in the center's cohort involves standardized outpatient clinic visits every two or three months according to the patient's age and the routine administration of pediatric vaccines through the Expanded Program on Immunization [15]. Moreover, vaccines that are specific to the management of children with SCD are also routinely given in the clinic, including pneumococcal, meningococcal and salmonella vaccines. This program also prescribes prophylactic oral penicillin V to all children aged 2 to 60 months, routine folic acid supplementation, and malaria prevention by intermittent treatment with sulfadoxine-pyrimethamine (SP) at the dose of ½ tablet for 10kg, once by month. The SP tablet contains 500mg of sulfadoxine and 25mg of pyrimethamine. All children reviewed in this study had a confirmed diagnosis of SCD by High Performance Liquid Chromatography (HPLC). Bacteremia, urinary tract infections, acute pneumonia, acute osteomyelitis, meningitis or meningoencephalitis, and acute cholecystitis were defined as severe infections. Blood and urine cultures were used for the detection of bacterial infections in febrile children within the cohort. The isolated bacterial strains were identified by biochemical and colorimetric manual methods. Sensitivity testing of bacterial isolates was performed against the betalactam, aminoglycoside, quinolone, and macrolide antibiotic groups. The resistance phenotypes were determined using a VITEK® 2 Compact device with an automated biochemical identification system using the antibiogram cards (AST-N222 and AST-N233). The quality control of the antibiotics tested was performed from the reference strain *E. coli* ATCC25922 (FDA Strain Seattle 1046). The diagnosis of pneumonia was based on clinical signs of lower respiratory tract infection and/or radiological assessment. Criteria for the diagnosis of acute osteomyelitis were clinical and radiological. A case of meningoencephalitis was diagnosed by CT scan imaging of the brain. All children with SCD were systematically screened for *P. falciparum* infection by Malaria Rapid Diagnostic Test (RDTs : Optimla-IT®), a Thick blood smear, and by polymerase chain reaction (PCR). Malaria was defined by the presence of asexual *Plasmodium* forms in blood or by PCR positivity on a frozen red blood cells pellet. The SD BIOLINE Malaria Ag P.f/Pan test was used for differential diagnosis between *P. falciparum* and other *Plasmodium species*. Children with confirmed malaria infection were hospitalized and treated with intravenous quinine, followed by oral artemisinin combination therapy. All of the identified *Plasmodium* strains were tested for their sensitivity to SP according to a standard technique [16]. We also tested for several common viral infections that are known to cause fever and other acute complications in children with SCD [17-19], including parvovirus B19, cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Nasal swab samples for bacterial culture were also obtained on all febrile children in the cohort. Routine evaluation of the complete blood count in the febrile patients was performed using an automatic ABX Micros 60 type meter (18 parameters). The study protocol was approved by the institutional ethics committee of CNESS (N°004/MS-SG-CNESS). All statistical analyses were performed using Statistical Package for Social Science (SPSS) version 25. The Chi2 test was used for statistical comparisons. Associations with $p < 0.05$ were considered to be significant. Qualitative variables were expressed in percentage and quantitative variables by position and dispersion parameters. The incidence of infections was expressed in person-months.

RESULTS

231 febrile children with SCD, aged from 6 months to 15 years, were included in the study: 183 SS (79.2%), 26 SC (11.3%), 12 S/β^0thalassemia (5.2%) and 10 S/β^+thalassemia (4.3%) phenotypes. This population represented 36.67% of the Center's pediatric recruitment. With 144 boys and 87 girls, the sex ratio was 1.65, and an age average was 93 ± 44 months. Table **1** shows the incidence of severe bacterial and *P. falciparum* infections. Urinary tract infections (5.2 cases per 1,000 person-years), bacteremia (1.4 cases per 1,000 person-years) and acute pneumonitis (1 case per 1,000 person-years) were the three major infections. Severe bacterial and *P. falciparum* malaria infections were significantly more common in SS patients than in other sickle cell patients (Chi2 = 7.67, p = 0.006). Table **2** shows the distribution of isolated bacterial strains on blood and urine cultures. Enterobacteria were much more common (28 strains/32; 87.5%). The most frequently isolated bacteria in blood and urine were Salmonella spp. and *E. coli* respectively. In one patient, *Salmonella spp* was isolated on both blood and urines cultures. *Streptococcus pneumoniae* and *Hemophilus influenzae* bacteremia were not observed. Isolated bacteria on

Table 1: Incidence of Severe Bacterial Infections and *P. Falciparum* Malaria According to Sickle Cell Phenotypes

Severe Infections	Sickle Cell Phenotypes				PM	IR (10^3PM)
	SS	SC	S/$\beta^{o\text{thalassemia}}$	S/$\beta^{+\text{thalassemia}}$		
Urinary tract infections (N=25)	18	2	4	1	4807	5.2
Bacteremia (N=7)	6	0	1	0	5005	1.4
Acute pneumonia (N=5*)	4	1	0	0	4928	1.0
Osteomyelitis (N=3)	2	1	0	0	5049	0.6
Acute cholecystitis (N=2)	2	0	0	0	5060	0.4
Acute meningoencephalitis (N=1)	1	0	0	0	5071	0.2
P. falciparum malaria (N=20)	14	2	2	2	4862	4.1

* 3 cases selected on clinical and radiological criteria, 2 cases selected on clinical criteria, PM : person-month, IR : incidence rate.

Table 2: Bacterial Strains Isolated in Blood and/or Urine

Bacterial Strains	Blood Cutures	Urines Cultures	Total
Enterobacteria (28 strains)			
E. coli	01	14	**15**
K. pneumoniae	01	04	**05**
Salmonella group	04	00	**04**
Enterobacter spp	00	02	**02**
Serratia ficaria	00	01	**01**
Raoultella ornithinolytica	00	01	**01**
No Enterobacteria (04 strains)			
Burkholderiacepacia group	01	00	**01**
Enteroccocus foecalis	00	03	**03**
Total	7	25	**32**

nasal swab samples were as follow: *Staphylococcus aureus* in 67 children (29%) with methicillin resistance profile in 2.6% of isolated strains, *Haemophilus influenzae* in 10 children (4.3%), *Granulicatella spp* in 6 children (2.6%), *Streptococcus pneumoniae* in 1 child (0.4%) and *Klebsiella pneumoniae* in 1 case (0.4%). The study of the sensitivity profile of isolated bacteria in blood and urine (Figures **1**, **2** and **3**) displays high levels of resistance against all classes of antibiotics except macrolides and quinolones. Extended spectrum betalactamases (*ESBLs*) and cephalosporinase were the two Most Common bacterial resistance phenotypes. *P. falciparum* malaria was found in 20 patients (8.6% of inclusions with 20% of submicroscopic forms). All strains of *P. falciparum* isolated had at least one mutation in the *PfDHPS* gene. Among the gene mutations, *G437 + S613* double mutation or triple mutation *(A634 / G437) + S613* were the most common combinations. The mutations observed in the *PfDHFR* gene most commonly involved double, triple, or quadruple mutations and combined the *R59, N108*, and *I51* mutants. The L164 mutation and mutant associations of the *PfDHPS* and *fDHFR* genes were most frequent. These mutants were triplet, quadruple, or quintuple. By the RT-PCR technique, infections with parvovirus B19, CMV, and EBV were found at frequencies of 30.7, 7.3, and 2.8% respectively. They were associated with severe bacterial infections or *P. falciparum* malaria at varying frequencies with association between them in the same patient (Table **3**).

In our study, severe bacterial infections and *P. falciparum* malaria were associated with two serious, life-threatening acute complications: acute chest syndrome (2 cases) and acute splenic sequestration (2

Table 3: Associations and Prognosis

Severe Infections	*P. falciparum*	EB19	CMV	EBV	Severe Acute Complication*
Urinary tract infections (N = 25)	3	9	4	7	
Bacteremia (N = 7)	0	2	2	3	-
Acute pneumonia (N = 5)	1	4	4	4	ACS (2 cas) ASS (1 cas)
Osteomyelitis (N = 2)	1	1	1	0	-
Acute cholecystitis (N = 2)	0	1	0	0	-
Acute meningoencephalitis (N = 1)	0	0	0	0	-
P. falciparum malaria (N=20)	-	4	1	4	ASS (1 cas)

* favourable course of all cases, ACS : acute chest syndrome, ASS : acute splenic sequestration.
EB19: Erythrovirus B19, CMV: Cytomegalovirus, EBV: Eptein Barr Virus.

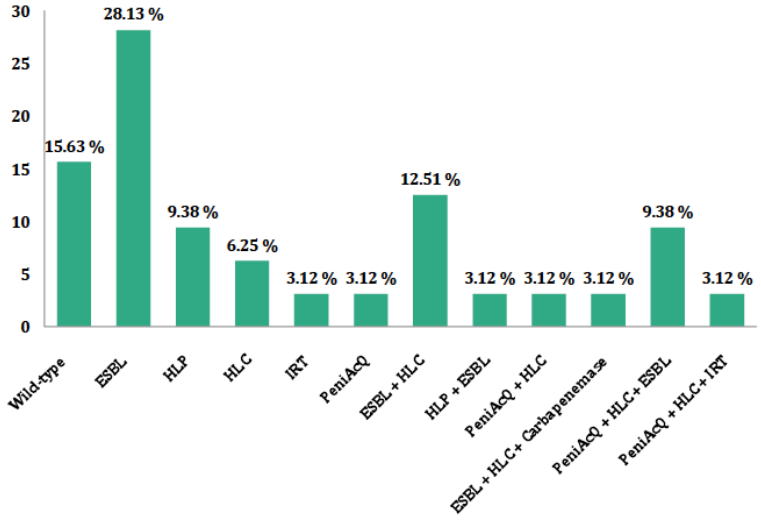

Figure 1: Betalactamine phenotypes resistance.
LLP: Low-level penicillinase, HLP : High level penicillinase, IRT : Inhibitors resistant, HLC : High-level cephalosporinase, ESBL : Extended Spectrum Betalactamase.

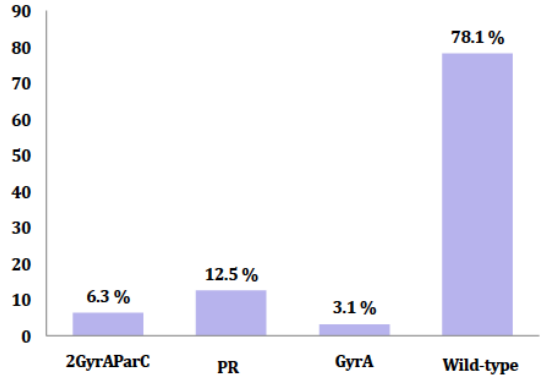

Figure 2: Quinolones resistance phenotypes.

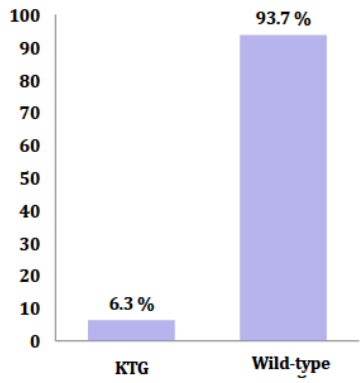

Figure 3: Macrolides resistance phenotypes.
Gyra : Higher or lower resistance, PR : Partial resistance, 2GyrAParC : High resistance level, K : Kanamicin, T : Tobramicin, G : Gentamycin.

cases). All of the children with severe complications ultimately survived.

DISCUSSION

To our knowledge, this report is the first to describe the incidence of severe infections in febrile children with SCD who received standardized specialty care in a referral center in sub-Saharan Africa. Within the background of this disease specific therapy, the three most common infections seen in the cohort were urinary tract infections, bacteremia, and acute pneumonia. The incidence rates observed for these complications were lower than those reported in

general pediatric population [6, 20, 21] or among children with SCD in the absence of regular follow-up [22]. We did not find *Streptococcus pneumoniae* or *Hemophilus influenzae* bacteremia as previously reported by Bansil in USA [23] and Rogovic in Canada [24]. Sickle cell patients studied by these authors, in addition to the patients reviewed in our cohort, had been immunized against *Streptococcus pneumoniae* and *Hemophlus inflenzae*. Thus, such a finding about the incidence rate of these infections could be attributed in part to the standardized immunization program. Previous studies have compared the incidence of invasive *Streptococcus pneumoniae* infections before and during the era of routine pneumococcal conjugate vaccines and found a significant reduction associated with vaccination [25-27]. Nevertheless, *Streptococcus pneumoniae* still remains the most important bacteria responsible for acute pneumonitis in children with SCD and should be respected in this regard [28]. In our study population, 1 patient was a nasal carrier of *Streptococcus pneumoniae*. Different studies have reported that pneumococcal vaccination does not prevent against all serotypes of *Streptococcus pneumoniae* [29, 30]. In our cohort, all children aged from 2 to 60 months had received prophylactic oral penicillin therapy. Adamkiewicz reported an incidence of invasive pneumococcal infections of 13.5 and 14.2 per 1000 person-years in SC and SS sickle cell children under 5 years respectively receiving routinely both 23-valent pneumococcal polysaccharride vaccination and oral penicillin V in 2008 in USA [31]. We did not find any studies on children with SCD vaccinated against pneumococcus who were also regularly receiving oral penicillin therapy in Africa. Our results encourage the strategy of systematic empiric antibiotic therapy with a third-generation cephalosporin in the case of fever in children with SCD [22,33]. However, the sensitivity profile of the bacteria isolated in urine or blood in patients within this cohort leads to the question of whether antibiotics with broader coverage should be used in the management of febrile children with SCD in our setting. In fact, among the antibiotics tested, the more active agents were the quinolones (78%) and macrolides (94%). For the population studied in this cohort, there seems to be an indication for the use of a broad spectrum cephalosporin in combination with either a macrolide or quinolone for empiric coverage of febrile patients. Incidence of acute osteomyelitis, meningitis, or acute cholecystitis were lower than those reported by Williams in Kenya [34], Akar in Kowet [35], Mava in Nigeria [36], and Koko in Gabon [37]. This difference can be explained by a difference in immunization status between our population and those studied by others. The immunization status of the children in these prior studies was not documented in all cases. In addition, these patients were not regularly followed in the context of organized specialty care. Few studies have been conducted on the association between common childhood viral infections in tropical environments and bacterial or malaria infections. In order to determine if these severe infections were the only causes of fever in children, we sought the coexistence of three common viral infections in children: EBV, CMV and parvovirus B19. For the first time, our study shows that co-infection with *P. falciparum* or a bacterial agent in combination with a viral infection with parvovirus B19, CMV or EBV is very common (45-84%) and thus underlines the multifactorial origin of fever in children with SCD in sub-Saharan Africa. Thus, our study highlights the need for in-depth studies on the etiologies of fever in the context of organized specialty care. All of the children within our cohort survived, despite the association between fever and other serious complications in 6% of patients This finding supports the idea that the prognosis for children with sickle cell disease depends largely on the access of patients to organized care [3] and supports the push for investment in specific programs that aim to improve diagnosis and management in countries with high prevalence of the sickle cell gene. Like other authors [38], we believe that adjusting the antibiotic regimen based on the sensitivity of the isolated bacteria is reasonable and may ultimately have an impact on reducing the incidence of bacterial resistance. The plasmodic index reported in our febrile sickle cell children was 7%, which is lower than that reported by others authors in Mali. In 2003, Dolo *et al*. reported a plasmodic index between 10 and 78%, depending on age and transmission season of the year in a rural population of Sudanese savannah children [39]. In an urban population of Malian children between the ages 3-59 months, Maïga *et al*. reported a plasmodic index of 28.9% and 12.4%, respectively before and after an intermittent chemoprophylaxis with amodiaquine and sulfadoxine-pyrimethamine [40]. These differences can be explained by different levels of endemicity between rural and urban areas [41]. Despite a low plasmodic index in our cohort, we observed multiple mutations (quadruple, quintuple and beyond) affecting the *PfDHPS* and *PfDHFR* genes. These mutations are responsible for treatment failure by sulfadoxine-pyrimethamine in cases of uncomplicated malaria [42]. These findings support the need to rethink the most effective chemoprevention regimen against *P. falciparum* malaria infection in sickle cell patients in Mali. Our study had several limitations. First, the pneumonitis diagnosis was most

often based on clinical signs and symptoms without the aid of radiographic findings. This diagnostic approach has the potential to overestimate the number of cases of acute pneumonitis. An additional limitation comes from the fact that only a single blood culture sample was obtained from the febrile children. This may have resulted in an underestimation of the incidence of bacteremia in this cohort. Despite these limitations, our study provides a unique look at severe bacterial infections and malaria in the context of febrile children with SCD regularly followed in an organized sickle cell care center in sub-Saharan Africa.

In conclusion, this study shows that a population of children with SCD receiving organized care in sub-Saharan Africa develops less severe bacterial or *P. falciparum* malaria infections than the general pediatric population. In our cohort, severe bacterial infections such as urinary tract infections, bacteremia and acute pneumonitis were more commonly caused by bacteria other than *Streptococcus pneumoniae* or *Hemophilus influenzae*. These severe bacterial infections were frequently associated with co-infection with common viral infections in children that we treated. We feel that the results of this study support the need to better characterize the etiologies of fever and to revise the standards of its management in children with SCD in sub-Saharan Africa. The efforts to develop more targeted antimicrobial strategies for this population of patients will likely reduce the expansion of resistance to antimicrobial agents in the future.

CONCLUSION

In order to prevent and control the emergence and spread of antimicrobial-resistant microorganisms, it is important to evaluate the impact of the use of prophylactic antimicrobial therapy within the context of a specialized sickle cell disease care model.

CONFLICTS OF INTEREST

Nothing to disclose. The authors declare no conflicts of interest.

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