Original Article

Prevalence of Serious Bacterial Infections in Children with Sickle Cell Disease at King Abdulaziz Hospital, Al Ahsa

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Abstract. *Objective:* The main aim was to report the prevalence and severity of serious bacterial infections (SBI) in children with sickle cell disease at King Abdulaziz Hospital (KAH), Al Ahsa, Saudi Arabia, to aid in determining whether outpatient management of such cases is appropriate.
Methods: We conducted a retrospective chart review of febrile children less than 14 years of age admitted with sickle cell disease 2005 through 2015.
Results: During 320 admissions, 25 children had SBIs (8%) including pneumonia (n=11), osteomyelitis (n=8), bacteremia (n=3, all with *Salmonella* species) and UTI (n=3). All recovered uneventfully.
Conclusion: It appears that in the current era, less than 10% of febrile children with sickle cell disease in our center are diagnosed with an SBI. Over 11 years, there were no sequelae or deaths from SBI. Given these excellent outcomes, outpatient ceftriaxone should be considered for febrile well-appearing children with sickle cell disease if they have no apparent source and parents are judged to be reliable.

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Introduction. Sickle-cell disease (SCD) is one of the most common monogenic disorders worldwide, characterized by wide variation in the associated disease's clinical manifestations and severity. SCD is most prevalent in Africa, the Middle East, the Indian subcontinent, and some Mediterranean countries.[1]

In Saudi Arabia, SCD was first reported in Eastern Province in the early 1960s. The prevalence varies significantly in different parts of the country but is highest in Eastern, followed by the southern provinces.[2]

Patients with SCD have an increased risk of invasive bacterial infections, particularly with encapsulated organisms including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Salmonella* spp. and *Escherichia coli*. The increased susceptibility to infections is related to many factors, primarily functional hyposplenism, and impaired opsonization. Other factors include genetic predisposition, mechanical risk factors, and abnormalities in the defense mechanisms, including an

abnormality in the alternative pathway of complement activities, and defective neutrophil function.[3,4]

An increased incidence of bacteremia in children with SCD has been well documented in the literature.[5,6] Fortunately, the incidence appears to have decreased following the introduction of routine childhood *H. influenzae* type B (Hib) and pneumococcal conjugate vaccines along with widespread use of prophylactic oral penicillin for young children with SCD[7-11] since it was proven to be effective in the late 1980s.[12] In one study, the introduction of pneumococcal conjugate vaccines resulted in an impressive reduction in invasive pneumococcal disease incidence by 90.8% in infants and 93.4% in children less than five years of age living with SCD.[13-16] Another study reported that the infection rate declined from 1.7 infections per 100 persons/year in 1995 to 2000 to just 0.5 infections per 100 persons/ year in the following two years in children ≤ 10 years of age.[17] However, other serious bacterial infections (SBIs), including pneumonia and acute osteomyelitis, continued to threaten SCD patients.

There are few studies of SBI among febrile children with SCD. A study from the United States reported that most had pneumonia.[18] The only previous study from Saudi Arabia was done before introducing HIB and conjugated pneumococcal vaccines.[19]

In terms of vaccines for encapsulated organisms in Saudi Arabia, the HIB vaccine was introduced nationally in 2002. Seven valent pneumococcal conjugate vaccines (PCV7) was introduced first in the Ministry of National Guard community only for high-risk children (aged <2 years) in 2006 and then for all children in that community in their first year of life starting January 2008. The program was expanded to include all Saudi children in January 2009. Thirteen valent pneumococcal conjugate vaccine (PCV13) was introduced in the national immunization schedule in January 2011. The current schedule includes four doses of HIB given at age 2,4,6 and 18 months, four doses of PCV13 given at the age of 2,4,6 and 12 months, and three doses of quadrivalent meningococcal vaccine (MCV4) given at nine and 12 months and 18 years of age.
https://www.moh.gov.sa/en/HealthAwareness/Educatio nalContent/HealthTips/Documents/Immunization-Schedule.pdf

The healthcare system is free of charge for all Saudis. There are two hematological centers under the Ministry of Health's charge located in two cities in Eastern Province (Al-Ahsa and Qatif) where sickle cell disease and thalassemia are prevalent.[20] However, patients can access any emergency room in any hospital in the province.

The KAH is the second-largest tertiary hospital in the Al-Ahsa area and was commissioned in late 2002 to provide healthcare for Saudi National Guard employees and their dependents. It is accredited by the Joint Commission of International Accreditation for Hospitals and has a 35-bed pediatric ward. Al-Ahsa is an oil and gas producing area located approximately 60 km inland from Arabian Gulf. It has 543,000 km^2 with a population of more than 1,220,655 (the year 2020).

Children with sickle cell disease are cared for in KAH by a hematologist in an outpatient clinic, and they have access to the emergency room for acute management. Our current guideline states that all children with sickle cell disease presenting with fever should be admitted to the hospital and follow a standard protocol for management. Parents are educated to pay meticulous attention to hygiene measures to reduce Salmonella infection risk for preventive measures. Parents are encouraged to monitor their children closely at home and seek advice if they have a fever or respiratory symptoms. The importance of compliance with vaccination and penicillin prophylaxis is reinforced during outpatient visits and inpatient admission. All children with sickle cell disease receive penicillin prophylaxis from diagnosis until the age of 5 years.

This study's main objective was to determine the current incidence rate and outcome of SBI in febrile Saudi children with SCD. If the incidence rate is relatively low and sequelae are rare, it may be safe to manage well-appearing febrile children with SCD as outpatients.

Methods. This study was based on a retrospective chart review of all patients younger than 14 years with SCD admitted to KAH 2005 through 2015 with a history of fever at home or a documented fever in the E.D.

Exclusion criteria were a) fever was not documented with a thermometer either at home or in hospital b) the patient had incomplete medical records. If a patient was discharged and then readmitted, this was recorded as multiple admissions.

A Febrile illness was defined as temperature ≥38°C measured by any method at any body site. Serious bacterial infections (SBI) were defined as bacteremia, meningitis, urinary tract infection, osteomyelitis, pneumonia, or bacteria's isolation from a normally sterile site. Urinary tract infections (UTI) has diagnosed if i) urine cultures grew more than 50 000 colony-forming units per milliliter of a single organism from a catheterized urine specimen or midstream urine and ii) pyuria was present (>5 WBC/HPF). Bacteremia was diagnosed if a common pathogen was recovered from one or more blood cultures or if an organism that is typical skin flora was recovered in two or more blood cultures. Meningitis was diagnosed if i) a true pathogen was recovered from the spinal fluid or ii) clinical examination in conjunction with CSF indices was suggestive of bacterial meningitis, but CSF was sterile as it was obtained after antibiotics had been administered. For children with suspected pneumonia, chest radiographs were interpreted by a radiologist

blinded to the suspected diagnosis. The diagnosis of pneumonia was then made by determining which of the following 3 categories best described the case: 1) Viral pneumonia: a) nontoxic child; b) proceeding upper airway symptoms (e.g. rhinorrhea, congestion; c) diffuse and bilateral auscultatory findings; d) bilateral diffuse interstitial infiltrate e) detection of a virus from the respiratory tract, 2) Bacterial pneumonia: a) ill or toxic appearing child; b) moderate or severe respiratory distress; d) focal or few auscultatory findings; d) imaging study showed any of the followings: lobar; segmental; or rounded consolidation; pneumatocele, cavitation, large pleural effusion, or necrotizing process; e) detection of bacteria that typically cause pneumonia from blood or another sterile site or 3) Atypical pneumonia: a) presence of constitutional findings including malaise, myalgia, headache, photophobia or sore throat; b) gradual and worsening nonproductive cough; d) diffuse crackles or wheezing on lung auscultation; d) presence of dermatological or extrapulmonary findings; e) diffuse or bronchopulmonary infiltrates . Acute chest syndrome (ACS) was defined as a new pulmonary infiltrate on chest radiograph, hypoxia (low blood oxygen concentration) accompanied by one or more of the following symptoms: fever, cough, dyspnea, or tachypnea. However, as there is an overlap with bacterial pneumonia, any patient who met both bacterial pneumonia and the ACS definition was considered to have either bacterial pneumonia or ACS. Osteomyelitis was diagnosed from reports of imaging studies in correlation with clinical findings. The diagnosis was considered to be confirmed if there was histopathologic evidence of inflammation in a surgical specimen of bone or identification of a pathogen by culture or gram stain in an aspirate of bone. The diagnosis was considered to be probable in a child with compatible clinical, laboratory, and/or radiologic findings in whom a pathogen was isolated from blood, periosteal collection, or joint fluid. The diagnosis was considered possible in a child with compatible clinical, laboratory, and radiologic findings with negative cultures (or not cultures obtained) and a response to empiric antimicrobial therapy.

The following data were collected from patient charts for each admission: age in months, gender, immunization status, presence of splenectomy and central venous line, previous hemoglobin electrophoresis results, use of hydroxyurea and penicillin prophylaxis before admission, compliance with penicillin prophylaxis (if applicable), reported temperature at home, E.D. triage vital signs, results of relevant cultures and radiographs and patient outcome. The data was recorded and coded in statistical software, SPSS 21 version.

Results. Three hundred twenty admissions met the

Table 1. Demographic characteristics for 320 admissions for febrile children with sickle cell disease.

Gender (N=320)	Male	185 (58%)
	Female	135 (42%)
Age M (±SD)		5.32 years (±2.91)
Number of admissions with fever (N=320)	Single admission	115 (36%)
	Multiple admission 2 admissions 3 admissions >=4 admissions	205 (64%) 23(11%) 19(9%) 23(11%)
Penicillin prophylaxis at time of admission (N=312)	Yes	238 (76%)
	No	74 (24%)
Vaccination Status (N=320)	Up to date for routine childhood immunization schedule	312 (98%)
	Data not available	8 (2 %)

eligibility criteria. Of them, 185 (58%) were male children (**Table 1**). The mean age at admission was 5±3 years. Fever was documented in the hospital for 106 admissions (33%) and only at home for 214 admissions (67%).

Of the 320 admissions, 115 children (36%) had a single admission for fever, while the others had multiple admissions (**Table 1**). All patients had homozygous sickle cell anemia except for 14 (4%) with sickle cell beta-thalassemia (SCD-Thalassemia); all were SB^0 type. Completed immunizations for age were documented for 312 admissions (98%) and were not documented for the remaining eight patients.

SBI was documented in 25 of the 320 admissions (8%; 95% CI 5.2-11.2%) (**Table 2**). No child was admitted more than once with an SBI. None of the patients with SBI had a CVL, one had a previous splenectomy, and 17 (68%) were male (**Table 3**). All patients with SBI had homozygous SCD and were fully immunized except for one child with SCD-Thalassemia and no immunization record available. The most common SBI was pneumonia (N=11; 4% of all admissions with 95% confidence interval ((CI) 2.0-

Table 2. SBI Prevalence in 320 admissions for febrile children with sickle cell disease.

Total (n=25)	No of Confirmed SBI Cases	Prevalence (%)	95% CI
Overall SBI Prevalence	25	8%	(5.2-11.2)
Pneumonia	11	3 %	(1.9-6.1)
Osteomyelitis	8	2.50%	(1.2-4.9)
Bacteremia	3	0.9 %	(0.2-2.7)
UTI	3	0.9 %	(0.2-2.7)
Meningitis	0	0	0

Legend: SBI: serious bacterial infection; UTI: urinary tract infection.

6.2%) of which 4 cases were presumed to be viral, and seven were bacterial versus ACS. Eight children (3% of all admissions; 95% CI 1.3-5.0%) had osteomyelitis (one confirmed, and seven possible cases). Blood cultures were obtained for 283 of the 320 patients during their admission (89%), of which 8 had positive cultures, but only 3 (1% of all admissions; 95% CI 0.3-2.8%) were thought to be true pathogens (all *Salmonella* species). None of the 37 patients without a blood culture obtained were diagnosed with an SBI.

All were well appearing except for the seven patients with bacterial pneumonia versus ACS; all were ill-looking and required admission to the intensive care unit; of them, one required mechanical ventilation. Seventeen children (66%) presented with severe neutropenia and leukocytosis (**Table 3**). All children survived to discharge.

For the 320 admissions, the child was on penicillin prophylaxis with suspected good compliance for 238 (74%), was not on penicillin, or compliance was thought to be low for 74 (23%), while data were not recorded for 8 (3%). SBI was diagnosed in 19 children on penicillin prophylaxis (8%) versus ten, not on penicillin (14%; p=0.15) (**Table 4**). Of the 19 children with SBI despite penicillin prophylaxis, three were vaccinated with 7 valent pneumococcal vaccine, and the remaining 16 were vaccinated with PCV13. Seven children out of 10 who were not on penicillin prophylaxis were vaccinated with PCV13, and the remaining three children had incomplete records.

Discussion. The overall prevalence of SBI in SCD

Table 3. Characteristics of Confirmed SBI Cases (n=25) in 320 admissions for febrile children with sickle cell disease.

Gender	Male	17 (68.0%)
	Female	8 (32.0%)
Mean Age	M(SD)	4.35 years (±2.78)
Absolute neutrophil count	Normal (>1500 mm3)	2 (8.0%)
	Mild Neutropenia (500-1500 mm3)	0
	Severe Neutropenia (<500 mm3)	17 (68.0%)
	Data not available	6 (24.0%)
White blood cells	Normal (4-12*10^9/L)	8 (32.0%)
	Leukocytosis (>12*10^9/L)	17 (68.0%)
	Leukopenia (<4*10^9/L)	0
Vital signs	Stable	25 (100%)
	Not stable	0
Hydroxyurea use at time of admission	Yes	5 (20.0%)
	No	20 (80.0%)
Previous splenectomy	Yes	1 (4.0%)
	No	24 (96.0%)

Legend. SBI: serious bacterial infection.

Table 4. Prevalence of SBI among patients on penicillin prophylaxis.

SCD Cases N=312	PP with suspected good compliance (overall prevalence) n=238	No PP or suboptimal compliance (overall prevalence) n=74	P-value
Confirmed SBI Cases	19 (8%)	10 (24%)	0.15
Pneumonia	5 (2 %)	6 (8 %)	0.01
Osteomyelitis	6 (2%)	2 (3 %)	0.93
Bacteremia	3 (1%)	0	0.13
UTI	1 (0.4%)	2 (3%)	0.15
Meningitis	0	0	0

Legend. PP: penicillin prophylaxis; SBI: serious bacterial infection; UTI: urinary tract infection.

patients admitted with fever was 8%, with 68% of SBI cases occurring in males. The most common manifestation was pneumonia, accounting for 3% of admissions.

A study from Qatif central hospital in the Eastern region of Saudi Arabia was conducted prior to introducing HIB and conjugated pneumococcal vaccines.[19] Of 450 admitted febrile and afebrile children, 39 (8.6%) had bacterial infections; *Salmonella* species predominated, and three children died (fatality rate 7.6%)[19] (Versus none in the current study). A recent study conducted in the Makkah region of Saudi Arabia reported that infection (but not necessarily SBI) was the second most common complication leading to admission in children with SCD, accounting for 9% of admissions but was dwarfed by the veno-occlusive disease, which accounted for 56% of admissions.[21]

Comparing to studies conducted in other countries, a 2013 study from the United States showed that the incidence of SBI in febrile children with SCD presenting to an E.D. was 16% (30 of 188) with 26 having pneumonia.[18] In a study conducted in Cameron of children with SCD hospitalized with suspicion of bacterial infection, the rate of SBI was 9.7%; as in our study, males predominated, accounting for 60% of cases.[22]

Pneumonia appeared to be the most common SBI in the current study, but the low incidence is presumably due to HIB and pneumococcal immunizations.[9,14,23] In children with SCD, the diagnosis of acute chest syndrome (ACS) is difficult to distinguish from pneumonia as both present with fever, cough, and pulmonary infiltrates on CXR, and it remains possible that some children diagnosed with pneumonia in the current study had ACS. Unless the blood cultures are positive, assigning an etiology to pediatric pneumonia is fraught with error, so etiologies were not analyzed in the current study. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were the most common causes of pneumonia in the Multicenter National Acute Chest

Syndrome Study (NACSS), followed by the respiratory syncytial virus (RSV), *Staphylococcus aureus,* and *Streptococcus pneumoniae*.[24]

As in previous reports, osteomyelitis was uncommon and typically accounted for less than 5% of SBI with SCD.[22,25,26]

Bacteremia was rare in the current study, accounting for only 3 SBIs in 320 admissions for fever; none of the patients with pneumonia or osteomyelitis were bacteremic. This datum differs markedly from studies in Africa, where 14%[5] and 28%[27] of febrile children with SCD were bacteremic. Although immunizations and penicillin prophylaxis may account for some improvement in the current study, it is noteworthy that many children in the African studies had pathogens such as *Klebsiella pneumoniae*[5] and *S. aureus*[27] that would not be impacted by these strategies.

The consensus is that children with SCD should receive penicillin prophylaxis until at least five years of age and potentially throughout childhood to prevent pneumococcal sepsis.[28] Not unexpectedly, many children in our study had SBIs despite penicillin prophylaxis, but it is striking that not a single child had pneumococcal sepsis (although some of the 11 pneumonia cases could have been pneumococcal). As the number of pneumococcal serotypes in conjugated vaccines increases, penicillin prophylaxis will become less useful, but it seems logical to continue it for now.

Although bacteremia was rare, all cases were due to *Salmonella* spp. A study from Cameroon also reported *Salmonella* spp to be the most common pathogens in bacteremic children with SCD.[22] A study in the Saudi population also revealed that Salmonella species were the leading cause of SBIs in SCD patients.[19] Unfortunately, available *Salmonella* vaccines are designed to cover only *S. typhi,* which likely accounts for a minority of Salmonella bacteremia cases in SCD.

Children with SCD are more inclined to develop UTIs than those without SCD. This tendency could be caused by altered blood flow in the renal vasculature, which causes papillary necrosis and loss of urinary concentration and acidification of the nephrons, resulting in dilute and alkaline urine favoring bacterial infection.[25] The children may develop compromised renal function due to recurrent UTI and repeated vaso-occlusive episodes;[23,29] Only three were admitted with UTI in the current study, but this may be because most children with UTIs are treated as outpatients even if febrile.

There were no cases of bacterial meningitis in the present study. In previously published studies from Saudi Arabia in the early 1990's the prevalence was 0.8% and 5.5%,[19,30] respectively. Organisms implicated were *S .pneumoniae, H. influenzae, N. meningitides,* and *Salmonella spp.*.[19,30] A low prevalence of meningitis has

also been reported in recent studies from Cameroon and Brazil.[22,31]

It is striking that there were only 25 cases of SBI diagnosed in the 11 years of this study, resulting in no deaths or apparent sequelae. Therefore, it would seem reasonable that well appearing febrile children in Saudi Arabia with reliable parents could be cultured, given antibiotics promptly, observed for at least a few hours in the emergency department, and discharged home with follow-up at 24 hours. Discharge following one dose of ceftriaxone has been studied in other countries. In the 1990s, this strategy was successful in 86[32] and 107[33] febrile episodes in children over six months of age in the U.S. The same regimen was also successful in 60 children in West Africa who had been febrile for < 36 hours.[34] In a more recent study from the U.S., about half of 390 cases were successfully managed as outpatients.[35] Although three patients managed as outpatients proved to be bacteremic in another U.S. study, all did well.[36] Given the low incidence of SBI in recent studies, perhaps antibiotics are not indicated in all children with fever and SCD. However, there is a need for further study of risk factors for and predictors of SBI before one could recommend withholding antibiotics.

This study's main limitation is that children could have had unrecognized SBIs that improved with empiric antibiotics. Our methodology would not have captured children who died of SBI before hospital admission. The retrospective analysis of data barred us from obtaining all the information necessary and having a control group to investigate factors driving the occurrence of SBIs. Data were collected from only one hospital.

Conclusions. The current prevalence of SBI in children with SCD appears to be much lower than previously reported, presumably due to penicillin prophylaxis and immunizations. It appears safe to consider empiric outpatient ceftriaxone therapy for well febrile children with SCD if they have a UTI or no apparent source and a reliable family.

Ethical consideration. This study was initiated after taking the ethical approval from the IRB of King Abdullah International Medical Research Center, Saudi Arabia. The identification of patients was kept anonymous, and data confidentiality was also ensured.

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