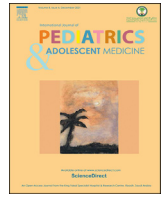


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## Incidence and predictors of bacterial infections in febrile children with sickle cell disease

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### ABSTRACT

**Introduction:** Sickle cell disease (SCD) is an autosomal recessive disorder. The incidence of bacterial infection in children with SCD globally is 16% compared 3–14% in general children. Bacterial infection in children is a severe problem and is considered to be a life-threatening condition. To reduce antibiotic overuse, the following factors might be associated with bacterial infection could help: age, C-reactive protein (CRP), white blood cells (WBCs) count, absolute neutrophil count (ANC), and genotype. Therefore, this study is designed to evaluate the CRP, ANC, WBCs, and platelet count levels as predictors for bacterial infection in febrile children with sickle cell anemia over a six-year period in a tertiary center in Jeddah, Saudi Arabia.

**Methods:** This study was a retrospective record review that included all SCD patients below the age of 18 years who presented with a febrile episode at any hospital's department from 2017 to 2019. Data were extracted from patient files that included culture result and the causative organism, CRP level, WBCs, ANC, and platelet count.

**Results:** The study included 62 children diagnosed with SCD who presented with 89 febrile episodes. There was no statistically significant difference in the median of CRP and ANC between the bacterial and nonbacterial febrile episodes ( $P = .314$ ,  $.735$ , respectively). However, the level of  $WBC > 20$  K/ $\mu$ L was statistically significant at  $P = .025$ .

**Conclusion:** WBCs significantly associated with a bacterial infection in SCD febrile children along with clinical assessments. This parameter can guide the physicians to determine the children at high risk of bacterial infection.

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### 1. Introduction

Sickle cell disease (SCD) is an autosomal recessive disorder that affects more than 250,000 children per year worldwide. The high prevalence is distributed among sub-Saharan Africa, the Mediterranean, and the Middle East [1]. The Saudi premarital screening program estimated that the prevalence of SCD in Saudi Arabia was 4.50%, which is the highest ratio among all Eastern Mediterranean countries [2,3].

This kind of inherited disorder had an impact on global public health authorities due to the associated high rates of morbidity and

mortality. Furthermore, the significance of the complications that developed in sickle cell patients ranging from vaso-occlusive crises that are associated with severe pain and organ damage and hemolytic anemia to a compromised immune system and hypo- or asplenic [4,5]. Such patients become more prone to suffer from multiple life attacks of several infections such as pneumonia, urinary tract infection, meningitis, and osteomyelitis [4].

The incidence of bacterial infection in children with SCD globally is 16% compared to 3–14% in general children [6]. Bacterial infection in children is a severe problem and considered a life-threatening condition. Despite the excellent prognosis and decreased incidence of morbidity and mortality in SCD in many countries due to the newborn screening, routine use of prophylaxis antibiotics, and the availability of vaccines against *S. pneumoniae*, *H. influenzae*, and influenza vaccines, and the premarital screening programs in Saudi Arabia, the bacterial infection has remained a high potential risk [7,8]. Sickle cell patients are often presented to

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the pediatric emergency department (PED) with fever due to either viral, bacterial infection, or sickle cell crises. The standard management in PED is use of an empirical broad-spectrum antibiotic for 48 h. After drawing a blood sample, it was cultured to determine whether it was a bacterial infection [9]. Although the bacterial culture results were rarely decisive [10], sepsis had a high risk of mortality in SCD patients [11].

The more the use of an unnecessary antibiotic for uncertain bacterial infection, the more the probability of bacterial resistance to occur, which is an outstanding challenge to global public health [12–14]. Therefore, finding a reliable predictor to discriminate between bacterial infection and other conditions is crucial for many reasons.

To reduce antibiotic overuse, the factors that might be associated with bacterial infection including age, C-reactive protein (CRP), white blood cells (WBCs) count, absolute neutrophil count (ANC), and genotype [15,16].

However, there are limited studies that examine the significance of (CRP) count and (ANC) as predictors for bacterial infection in febrile children with SCD and demonstrated the incidence of such diseases. Therefore, this study is designed to evaluate the CRP and ANC levels as predictors for bacterial infection in febrile children with sickle cell anemia over a six-year-period in a tertiary center in Jeddah, Saudi Arabia. Other predictors such as WBCs and platelet counts were also evaluated.

## 2. Methodology

A retrospective record review was conducted in 2019, included all SCD patients below the age of 18 years who presented with a febrile episode at any hospital's department from 2017 to 2019.

The febrile event was defined as a presentation of 38°C or higher. SCD was defined as homozygous sickle cell anemia alone, with sickle-hemoglobin C or with sickle-thalassemia. We excluded those who were immunocompromised due to another medical illness or immunosuppressant medications in addition to those who had incomplete medical records.

The data were obtained from the electronic medical record of the Phoenix system and entered Microsoft excel sheet, which included abstracted descriptive data such as age, nationality, type of SCD, immunization status, use of prophylactic antibiotic, and surgical splenectomy. In addition, pressure, heart rate, need of admission, and duration of access were monitored. Furthermore, the diagnostic data included culture results and the causative organism, CRP level, WBCs, ANC, and platelet count.

SPSS software version 25 was used to analyze the data through chi-square statistically, correlation, and independent sample *t*-test for bivariate variables while using frequency and descriptive for univariate variables.

## 3. Results

### 3.1. Children's clinical picture

Over six years (2013–2018), 62 children diagnosed with SCD presented with a total of 89 febrile episodes. Of these children, 46.9% were Saudi and 53.1% were non-Saudi patients. Eighty percent of the cases known to have the homozygous type of SCA, while the remaining 20% had sickle-thalassemia type. Specific bacterial infection was recorded in 9% ( $n = 8$ ) of the febrile episodes, including *Enterococcus faecium*, gram-negative coccobacilli, coagulate-negative staphylococcus, *Klebsiella*, *Enterococcus faecalis*, *Streptococcus viridians*, and acid-fast bacillus). The age of these children was 3, 5, 5, 2, 7, 10, 2, 9 years, respectively. The mean age of all febrile SCD cases was (8.32 years, SD 4.30); the cases confirmed

to have bacterial infection and nonbacterial febrile episodes were (5.375 years, SD 3.06) and (8.414 years, SD 4.24). The percentage of episodes presented with splenectomy was 6.3% from 79 episodes, with no available data in the remaining 10 episodes. Also, because of limited medical records, there was no documentation about the new vaccination status in all patients. No significant variation between the presence of bacterial infection and type of hemoglobinopathy ( $P = .571$ ), or length of hospitalization ( $P = .575$ ). The median length of stay was seven days (IQR = 8.75 days); it significantly varied with age ( $P = .052$ ).

### 3.2. Predictors of bacterial infection

The count of WBCs, CRP, ANC, and platelets was collected from the first day of admission; the median of WBCs, CRP, and ANC was (17.2800, IQR = 11.15), (52.5500, IQR = 61.15), and (37.4950, IQR = 73.81) respectively, while the mean platelet count was (348.8243, SD 9.419). There was no statistically significant difference in the median of CRP and ANC between the bacterial and nonbacterial febrile episodes ( $P = .314$ ,  $.735$ , respectively). Platelet count did not significantly vary between the two groups ( $P = .08$ ). There was a significant variation in WBC ( $P = .025$ ).

## 4. Discussion

This study was designed to evaluate the CRP, ANC, WBCs and platelet count levels as predictors for bacterial infection in febrile children with sickle cell anemia over a six-year-period in a tertiary center in Jeddah, Saudi Arabia.

In this study, the rate of bacterial infection among all the episodes presenting with fever of 38.5 °C or higher was 8.6%. This was considered to be the highest rate compared to other studies in the same domain, for example, a study conducted in London, UK, with a rate of 3.4% [17]. There is no frequency in the type of organism more than one in our results, while in previous two studies, *Salmonella* species was the most universal identified organism [15,18]. Clinical diagnosis of bacterial infection is complicated, and there is no clear cut off laboratory findings other than culture results to differentiate between bacterial and viral infections.

Platelet count did not significantly indicate bacterial infection in children with SCD presenting in the emergency department with a fever of 38.5 °C or higher more besides the clinical assessment, according to this study. Furthermore, our results indicate relatively good sensitivity and specificity for bacterial infection with a count of WBC 20 K/ $\mu$ L. A previous study found that a high level of CRP (CRP of 100.0 mg/L) is strongly associated with a bacterial infection in SCD patients [15]. In addition, in another study, they showed an association of the ANC (ANC 20  $\times 10^9$ /L) with the specificity of 88% with a bacterial infection in those children [16]. Another study in 2002 in California showed that the independent association of WBC, ANC, and absolute band count (ABC) with bacteremia in febrile children with SCD [17].

All these parameters can be considered as a risk factor for bacterial infection in febrile SCD children presented in the emergency room in the form of guidance for health care providers to assess and treat the patients either as outpatients or inpatients according to other parameters such as nontoxic general appearance and hemodynamic stability. Patients with low risk of bacteremia can be managed as outpatients to avoid the deterioration of symptoms and the risk of increase fever in the hospital staying. High-risk patients should be admitted and treated with empirical antibiotics and standard management. According to our results, there is no significant variation in the median length of hospitalization between the febrile bacterial episodes (10 days) and nonbacterial febrile episodes (7 days).

Our present study has some limitations: small sample size, gaps in the documented data such as new vaccination status and administration of antibiotic prophylaxes in patients' profiles, and the absence of some laboratory tests in few episodes. This explains the needs of other more extensive and robust supported studies with a large sample size and prospective nature in our community for more details and to enhance and emphasize our study findings with the intent to improve the health quality in this group of patients.

## 5. Conclusion

In conclusion, WBCs was a significant predictor in febrile SCD patients indicating bacterial infection that can guide the physicians to determine the children at high risk of bacterial infection.

## Ethical statement

This study was approved by the IRB at King Abdulaziz University. No human or subject experiments in this study.

## Visual abstract

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpam.2020.12.005>.

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