Original Article

DOI: 10.7860/JCDR/2023/66152.18460

Paediatrics Section

Frequency and Patterns of Bacteraemia in Children with Sickle Cell Disease: A Prospective Cohort Study

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ABSTRACT

Introduction: Sickle Cell Disease (SCD) is one of the most common inherited haemoglobinopathies and is associated with high morbidity and mortality, particularly in early childhood among the affected population. Infection is a significant contributor to morbidity and mortality in SCD.

Aim: To investigate the frequency and pattern of bacteraemia in children with SCD.

Materials and Methods: This prospective cohort study was conducted in the Department of Paediatricss at Acharya Vinoba Bhave Hospital, Sawangi (M), Wardha, Maharashtra, India, a tertiary care hospital attached to Jawaharlal Nehru Medical College from October 2019 to September 2021. A total of 70 patients with SCD, aged upto 18 years, who presented with fever on two separate occasions and were admitted to the hospital, were included in the study. Blood culture, complete blood counts, and C-reactive Protein (CRP) tests were conducted to detect bacteraemia immediately after admission and when required. Quantitative data was analysed using mean, median, and standard deviation.

Results: In the present study, out of 70 patients, 40 (57.14%) were male and 30 (42.86%) were female. A total of 54 (77.14%) were homozygous and 16 (22.86%) were heterozygous for SCD. A total of 30 (42.86%) patients belonged to the 6-10 years age group. Fever and pallor were the most common clinical findings. The rate of bacteraemia was found to be 15.71%. Gram-negative organisms were more frequently isolated compared to gram-positive isolates. The most common organism isolated in sickle cell patients was *Klebsiella* species (36.36%).

Conclusion: Bacteraemia was observed in only approximately 15.71% of the patients. Gram-negative bacteraemia was more prevalent in patients with SCD. Patients with acute chest syndrome were more susceptible to bacterial infections. Mortality was higher in sickle cell patients from whom organisms were isolated in blood cultures.

Keywords: Blood culture, Crisis, Fever, Gram-negative bacteraemia, Haemoglobinopathies

INTRODUCTION

Haemoglobinopathy is the most common monogenic disorder in India. Of these haemoglobinopathy, α thalassaemia is seen in all communities, but SCD is more prevalent in the malaria endemic zone [1]. It is more commonly seen among people of Africa, Southeast Asia, and Middle East countries [2]. SCD is an important contributor to under-5 mortality in low and middle-income countries [3]. The prevalence of sickle haemoglobin varies between 0-40% in India. The affected regions include Central India, Vidarbha region of Maharashtra, Kerala, Orissa, south Madhya Pradesh, and Eastern Gujarat [4]. Sickle cell anaemia can be life-threatening due to its acute or chronic complications such as vaso-occlusive crisis, acute chest syndrome, sequestration crisis, stroke, pulmonary hypertension, and infection [5]. The crises are often preceded by stressful events such as fever, infection, hypoxia, emotional upheaval, and dehydration [6]. However, in most patients, no obvious factor precedes the crisis [7].

Bacterial infections are one of the most prevalent complications faced by patients with SCD and can present as both acute or chronic conditions. They contribute to the morbidity and mortality rate, affecting both younger and older age groups [5]. Sickle cell anaemia patients are at risk of infection due to functional asplenia or hyposplenia, mechanical factors, and complement system dysfunction [5]. The most common presentation of bacterial infection remains fever. Additionally, fever induced by bacteraemia in children with SCD is often misdiagnosed as a vaso-occlusive crisis [8]. The detection of the causative organism remains a major challenge, as some of the previously detected causative organisms are fastidious and slow-growing [9].

Therefore, the present study was conducted to explore the frequency and patterns of bacteraemia in children with SCD and to study the causative organism and its outcome. This will help us understand the primary causes of infections in Indian population, and additional measures can be taken to overcome this morbidity and mortality.

MATERIALS AND METHODS

This prospective cohort study was conducted in the Department of Paediatricss at Acharya Vinoba Bhave Hospital, a tertiary care hospital attached to Jawaharlal Nehru Medical College, Sawangi (M), Wardha, Maharashtra, India, from October 2019 to September 2021. The study was conducted after obtaining clearance from the Institutional Ethics Committee (IEC number: DMIMS/DU/IEC/2021/562). Informed written consent was obtained from the parents or guardians of the patients who were willing to participate in the study.

Inclusion criteria: All patients under 18 years of age who had previously been diagnosed with SCD and were currently admitted to the Paediatrics ward with a fever higher than 100°F on two separate occasions during this admission, as well as febrile patients newly diagnosed with SCD during the admission, were included in the study.

Exclusion criteria: Patients who were admitted for prophylactic blood transfusion, SCD patients presenting with conditions other than fever, and patients attending only the outpatient department were excluded from the study.

Study Procedure

All essential data, including demographic information such as age, sex, and residence, were recorded. Sickling pattern was confirmed

by High Performance Liquid Chromatography (HPLC), and detailed history about symptoms during presentation and socioeconomic status was noted. Physical examinations, such as assessment of pallor, icterus, temperature, peripheral oxygen saturation, respiratory rate, and joint examination, were performed and recorded in a pre-designed proforma. The Modified BG Prasad socioeconomic scale was used to determine socioeconomic status [10]. A 5 mL blood sample was collected by venipuncture under aseptic precautions upon admission before starting antibiotics. The collected blood was transferred to a BACTEC bottle for Paediatrics use. The needle was changed before puncturing the bottle. The sample was processed in the hospital's microbiology laboratory using the automated BD BACTEC blood culture system within one hour of collection. Investigations for detecting bacteraemia, such as blood culture, complete blood counts, and CRP, were performed immediately after admission and repeated as needed.

Definitions used:

- Bacteraemia: Fever with isolation of bacteria from the blood [11].
- Vaso-occlusive crisis: "The new onset of pain that lasts at least four hours for which there is no explanation other than vasoocclusion and requires therapy with parenteral opioids or ketorolac in a medical facility [7]."
- Acute chest syndrome: "A severe form of sickle cell crisis manifesting as a new pulmonary infiltrate involving at least one complete lung segment consistent with alveolar consolidation accompanied by chest pain, fever (>38.5°C), tachypnoea, and wheezing or coughing [7]."
- Haemolytic crisis: Sudden drop in haemoglobin, jaundice [7].
- Mixed crisis: Overlap of two or more of the above crises [12].
- Tachypnoea: "The definition of tachypnoea is related to age, with a respiratory rate of >60 breaths/min in infants aged 0-2 months, >50 in infants 2-12 months, >40 in children 1-5 years, and >20 in children >5 years of age" [13].

STATISTICAL ANALYSIS

All data were entered into Microsoft Excel spreadsheets. Descriptive and inferential statistical analyses were performed using Stata software (Stata 10, Stata Corporation, Texas, USA). Quantitative data were analysed using measures such as mean, median, and standard deviation. Data were analysed based on the assigned groups. Normally distributed continuous data were compared using the Student's t-test, and the Mann-Whitney U test was used for skewed data. The chi-square test or Fisher's exact test was used for analysing qualitative data. Differences between means were compared using unpaired Student's t-test. A p-value less than 0.05 was considered statistically significant.

RESULTS

In the present study, a total of 70 Paediatrics admissions were included, of which 54 belonged to homozygous sickle disease and 16 were of heterozygous sickle disease. There were 40 (57.14%) males and 30 (42.86%) females affected by the sickle cell disorder, with a male:female ratio of 1.3:1. Among the patients, 14 (20%) were in the 0-5 years age group, while 26 (37.14%) and 30 (42.86%) belonged to the 6-10 years and >10 years age groups, respectively. Only 20 (28.57%) of the patients received hydroxyurea, and none of the sickle cell trait patients received hydroxyurea [Table/Fig-1]. The majority of patients presented with isolated fever or fever with symptoms other than crisis (e.g., burning micturition, rash, running nose, sore throat, etc.), followed by fever with joint pain, fever with breathlessness, fever with jaundice, fever with joint pain and breathlessness, fever with breathlessness and jaundice, and fever with joint pain and jaundice [Table/Fig-2].

Among the studied population, 20 (28.57%) patients had a history of consanguinity. Clinical examination revealed pallor in 49 (70%) patients, icterus in 24 (34.28%) patients, splenomegaly in 28 (40%) patients, and malnutrition in 21 (30%) patients. Blood culture was positive in 11 (15.71%) patients. When various parameters such as history of consanguinity, pallor, icterus, splenomegaly, malnutrition, and bacteraemia were compared between the homozygous and heterozygous groups, they were all statistically significant, except for malnutrition and bacteraemia [Table/Fig-3].

Characteristics		n (%)
Gender	Male	40 (57.14)
	Female	30 (42.86)
Sickling pattern	Homozygous	54 (77.14)
	Heterozygous	16 (22.86)
Age (in years)	<5	14 (20)
	6-10	26 (37.14)
	>10	30 (42.86)
Socioeconomic status	Upper class (I, II)	10 (14.28)
	Middle (III, IV)	28 (40)
	Lower (V)	32 (45.72)
Area of residence	Rural	48 (68.57)
	Semiurban	14 (20)
	Urban	8 (11.43)
Antibiotic before taking culture	Received	21 (30)
	Not received	49 (70)
Hydroxyurea	Received	20 (28.57)
	Not received	50 (71.43)
SpO_2 at room air	<94	13
	≥94	57
Respiratory rate	Tachypnoea	21 (30)
	No tachypnoea	49 (70)

[Table/Fig-1]: Demographic data of study population (N=70).

Symptoms	n (%)
Isolated fever (or with symptoms not related to crisis)	31 (44.28)
Fever with joint pain	15 (21.42)
Fever with breathlessness	9 (12.85)
Fever with jaundice	7 (10)
Fever, joint pain, breathlessness	4 (5.71)
Fever, breathlessness, joint pain	1 (1.42)
Fever, joint pain, jaundice	3 (4.32)

[Table/Fig-2]: Presenting complaints of patients (N=70).

Characters	Homozygous (n=54) n (%)	Heterozygous (n=16)n (%)	p-value (Chi-square test)
Pallor	41 (75.92)	8 (50)	0.04
Icterus	23 (42.59)	1 (6.25)	0.0016
Splenomegaly	25 (46.29)	3 (18.75)	0.049
Malnutrition	17 (31.48)	4 (25)	0.6
Consanguinity	19 (35.1)	1 (6.25)	0.02
Bacteraemia	9 (16.7)	2 (12.5)	0.6

[Table/Fig-3]: Comparison of various characteristic between homozygous and heterozygous group.
Chi-square test

Bacteraemia was observed in 11 admissions, and when compared with the culture-negative group, CRP levels were significantly higher in the culture-positive group. The mean duration of stay was 7.81±10.35 days in the culture-negative patients and 10.09±9 days in the culture-positive patients. Among both groups, haemoglobin, TLC, neutrophils, platelet count, and hospital stay were statistically insignificant [Table/Fig-4]. Among the 11 participants with culture growth, 7 (63.63%) had growth of gram-negative organisms, while

gram-positive organisms were observed in 4 (36.36%) patients. Among them, 4 (36.36%) patients had *Klebsiella* species growth. *Pseudomonas* and *Staphylococcus* species were observed in 3 (27.27%) patients each, and *Streptococcus* species growth was observed in 1 (9.09%) patient [Table/Fig-5].

Investigations	Culture negative (Mean±SD)	Culture positive (Mean±SD)	p-value (t-test)
Haemoglobin (mg/dL)	8.22±2.40	7.63±3.05	0.4
TLC (cells/µL)	13254.58±9030.42	16676±9517.21	0.2
Neutrophils (cells/µL)	58.84±14.98	60.18±17.43	0.7
Platelets (cells/µL)	2.30±1.51	2.59±1.76	0.56
CRP (mg/dL)	14.25±19.99	30.16±34.40	0.03
Hospital stay (days)	7.81±10.35	10.09±9	0.4

[Table/Fig-4]: Comparison of investigation findings and hospital stay among culture positive and negative patients.
TLC: Total leukocyte count; CRP: C-reactive protein

Gram +ve (n=4)		Gram -ve (n=7)		Total (N=11)
Staphylococcus	*Streptococcus*	*Klebsiella*	*Pseudomonas*	
3	1	4	3	11

[Table/Fig-5]: Distribution of organism isolated from patients.

Out of the total 11 participants with organism growth in their cultures, only 2 (18.18%) had not received prior antibiotics, while the other 9 (81.82%) had received prior antibiotics. Among the 70 admissions, 31 presented without any crisis, 31 (44.28%) presented with one of the crises, and 8 (11.42%) presented with an overlap/mixed of various crises [Table/Fig-6]. When the association of crisis was examined with the culture-positive group, no significant association was found between these two parameters [Table/Fig-7].

Crisis	Culture negative (n=59) n (%)	Culture positive (n=11) n (%)	Total (N=70)
No crisis	27 (45.76)	4 (36.36)	31 (44.28)
Vaso-occlusive crisis	14 (23.73)	1 (9.09)	15 (21.42)
Acute chest syndrome	5 (8.46)	4 (36.36)	9 (12.85)
Haemolytic crisis	7 (11.86)	0 (0)	7 (10)
Mixed	6 (10.16)	2 (18.18)	8 (11.42)

[Table/Fig-6]: Distribution of various crisis among culture positive group.

Sickle cell crisis	Culture -ve	Culture +ve	Total	p-value (Chi-square test)
No	**27**	**4**	**31**	**0.56**
Yes	**32**	**7**	**39**	
Total	**59**	**11**	**70**	

[Table/Fig-7]: Association of sickle cell crisis with bacteraemia.
Statistical test used- Chi-square test

Out of the 54 homozygous patients, only 20 were receiving hydroxyurea. The association of hydroxyurea with episodes of sickle cell crisis was not found to be statistically significant [Table/Fig-8].

Hydroxyurea	Sickle cell crisis	No sickle cell crisis	Total	p-value (Chi-square test)
Received hydroxyurea	17	3	20	0.10
Not received hydroxyurea	22	12	34	
Total	39	15	54	

[Table/Fig-8]: Association of sickle cell crisis with hydroxyurea.
Chi-square test was used

A total of 4 (36.36%) of the patients with growth in their cultures did not develop any crisis, while 5 (36.36%) of them developed acute chest syndrome alone. Additionally, 2 (18.18%) had vaso-occlusive crisis with super-added haemolytic crisis. One (9.09%) patient with growth in their culture had an isolated vaso-occlusive crisis. All deaths observed occurred only in patients in whom the culture was reported to be positive. Out of the total 11 patients with growth of organisms seen, 2 (18.18%) succumbed to death, while the other 9 (81.81%) were discharged from the hospital after successful management. This difference observed was statistically significant, with a p-value of 0.001.

DISCUSSION

Sickle cell disease (SCD) is an autosomal recessive disease that occurs due to the substitution of valine for glutamic acid at the 6th position of the beta-globin gene. Patients with homozygous HbS gene are diagnosed with SCD, while those with heterozygous HbS gene are referred to as having sickle cell trait [14]. SCD can manifest as homozygous (SS), heterozygous (AS), or other heterozygous forms, such as sickle thalassaemia. Sickle cell anaemia (SS) is more symptomatic than sickle cell trait (AS) and presents with various manifestations such as dactylitis, swelling, and pain in large joints, body ache, abdominal pain, headache, neurodeficit in the form of motor weakness, anaemia, jaundice, etc. Patients may exhibit signs of anaemia, icterus, splenomegaly, hepatomegaly, or both, along with features of crises such as vaso-occlusive crisis, aplastic crisis, sequestration crisis, and haemolytic crisis. The SCD can present with a wide variety of clinical manifestations. Fever without a source in a sickle cell patient is considered a medical emergency as it increases the possibility of bacterial infection, which can subsequently lead to a high mortality rate. Every febrile sickle cell child needs to undergo thorough investigation for bacterial infection.

In the present study, there were 54 admissions with homozygous sickle disease and 16 with heterozygous sickle disease. Among them, a total of 40 (57.14%) males and 30 (42.85%) females were affected by the sickle cell disorder, resulting in a male:female ratio of 1.3:1. The male:female ratio in SCD was 1.7:1, while in the trait group, it was 0.6:1. Similar findings were observed in a study conducted by Alima Yanda AN et al., where males (58, 60.4%) were more affected than females (38, 39.4%) [5]. Mandot S and Ameta G found a male:female ratio of 3.6:1 in SCD patients and 1.38:1 in those with sickle cell trait, which did not match with the present study [15]. This difference can be attributed to the fact that their study aimed to document the prevalence of sickle cell anaemia only among the scheduled tribe (Garasia) of Sirohi district in Rajasthan state, which has an unequal gender distribution. Among the total study population of 70 individuals, 14 (20%) belonged to the 0-5 years age group, while 26 (37.14%) and 30 (42.86%) belonged to the 6-10 years and >10 years age groups, respectively. Thus, the majority of children in the study belonged to the >10 years age group. This finding is consistent with a study conducted by Vieira AK et al., [16]. Yadav R et al., stated that the majority of children (30.2%) belonged to the 5-10 year age group, compared to 21% in the 10-15 year age group and 19.3% in the below five years age group [17]. The presenting age in the present study is higher compared to other studies, as the index cases are from a hospital that serves a rural geographic area where awareness, literacy rates, and the tendency to seek medical advice from a health facility are lacking. The other studies mentioned were conducted in urban areas [12,18,19].

The present study findings revealed consanguinity in 19 (35.19%) of the homozygous group and only 1 (6.25%) participant in the heterozygous group. This data was statistically significant, and similar conclusions can be drawn from various other studies [12,18,19]. The majority of the index patients belonged to Scheduled Caste (SC) or Scheduled Tribes (ST). Similar findings were noted in a study from Gondia district in Maharashtra [20]. The majority of the present study population was from rural areas with low socioeconomic status. It is difficult to infer whether socioeconomic status plays a role in the clinical outcome of the disease from the present study due to the small sample size. However, it is proven that lower socioeconomic status increases the prevalence of SCD, the risk

of complications, the number of hospital admissions, and lowers health-related quality of life [21].

Almost 30% of the study population received intravenous or oral antibiotics before being investigated for bacteraemia. This use of antibiotics may reduce the rate of culture positivity. Hydroxyurea was prescribed only to homozygous patients, and only 37% of homozygous patients received it. The association between hydroxyurea and the frequency of sickle cell crisis was found to be statistically insignificant. This is contradictory to other studies that have shown that hydroxyurea reduces the episodes of painful crisis and the need for blood transfusions [22,23]. This discrepancy could be due to lower compliance, as hydroxyurea is a costly drug and the majority of our study population comes from rural areas with low socioeconomic status. Splenomegaly was observed in 25 (89.29%) of the homozygous and 3 (10.71%) of the heterozygous study participants out of the total of 28 children. The differences observed in the data for pallor, icterus, and splenomegaly were statistically significant. The present study revealed pallor in 70%, icterus in 24 (34.28%), and splenomegaly in 28 (40%) of the participants. The results for pallor and splenomegaly were comparable to a study conducted by Mandot S and Ameta G but present study showed icterus in only 3.25% of patients [15]. This variation can be attributed to differences in the study population. In the present study, 77% of the population was homozygous, and icterus is a more predominant feature of the homozygous variety of sickle cell disease.

Fever and infection can be precipitating factors for various crises, but a significant association was not found in the present study. Vaso-occlusive crisis was present in 15 (21.42%) participants, acute chest syndrome in 9 (12.85%), and haemolytic crisis in 7 (10%), with 8 (11.42%) experiencing a mixed crisis. These findings are consistent with studies by Kamble M and Chatruvedi P and Wierenga KJ et al., [12,24]. Wierenga KJ et al., observed that painful crisis occurred in 45 (27.3%) of the events, with 20 being isolated findings and the other 25 being associated with other conditions such as acute chest syndrome [24].

The present study's results showed that bacteraemia was seen in only 11 patients who had a fever. Similar studies have shown bacteraemia rates ranging from 9% to 20.8% [19,25,26]. In contrast, a study by Al Salman J et al., from Bahrain showed bacteraemia in 46.67% of patients [27]. These variations in blood culture positivity could be due to various factors, such as differences in methods of blood culture specimen collection and the use of prior antibiotics. Gram-negative bacteraemia was predominant in the present study, which is consistent with findings from various other similar studies [24,25,28]. The organisms grown in blood cultures were variable, with commonly isolated gram-negative bacteria including *Klebsiella* and *Pseudomonas* species, while gram-positive cultures often included *Staphylococcus* and *Streptococcus* species. The most common isolated species in blood cultures varies in various studies. In the present study, *Klebsiella* species were the most common, accounting for 36.36% of isolates. Similar findings were noted in other studies, ranging from 26% to 59% [29,30]. However, other studies have reported *Staphylococcus aureus* [25] and *Streptococcus pneumoniae* [24] as the most common isolates. Wierenga KJ et al., noted that out of 10 isolates, 3 (30%) were *Streptococcus pneumoniae*, H. influenzae constituted 20%, and the remaining 50% were gram-negative bacteria [24]. Lalhmunsangi J et al., reported *Staphylococcus aureus* (20.23%), E. coli (19%), *Klebsiella* pneumoniae (15.47%), and *Pseudomonas* (9.52%) as the most common isolates [25]. Brown B et al., observed *Klebsiella* pneumoniae (25%) and *Staphylococcus aureus* (25%) [26].

In the present study, 4 (36.36%) patients with growth in their cultures did not develop any crisis, while 4 (36.36%) developed acute chest syndrome alone, 2 (18.18%) had vaso-occlusive crisis with super-added haemolytic crisis, and 1 (9.09%) patient with growth in their culture had an isolated vaso-occlusive crisis. These findings were statistically significant. Vichinsky EP et al., observed that the most frequent complications during vaso-occlusive crisis episodes were infectious diseases (25.9%), fever (21.8%), and pulmonary disorders (16.2%) [31].

The present study findings revealed that both deaths observed were in patients where the culture was reported to be positive. Among the total of 11 patients with growth of organisms in their cultures, 2 (18.18%) died, while the other 9 (81.81%) were discharged from the hospital after successful management. This difference was statistically significant. Akuse RM stated that 12 (80%) of the 15 patients who died had infection [28].

Limitation(s)

The present study specifically evaluates bacteraemia as a cause of febrile episodes in SCD. Other bacterial infections, viral illnesses, and parasitic infections were not studied. It is important to note that many of the study participants received antibiotics prior to admission in the hospital or in the outpatient department, which could have affected the detection of the organisms in the culture media.

CONCLUSION(S)

In the present study, prevalence of bacteraemia in children with SCD admitted to our rural hospital was found to be 15.71%. Gram-negative organisms were found to be responsible for the majority of the infections, with *Klebsiella* species being the most commonly isolated organism, followed by *Pseudomonas*, *Staphylococcus*, and occasionally *Streptococcus* species. Among the patients with positive blood cultures, fever and pallor were the most common clinical findings on admission. Bacteraemia was predominantly seen in sickle cell children who presented with acute chest syndrome at the time of admission. Deaths were observed only in those patients where blood culture reports were found to be positive.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 21, 2023
- Manual Googling: Jul 25, 2023
- iThenticate Software: Aug 15, 2023 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jun 20, 2023**
Date of Peer Review: **Jul 19, 2023**
Date of Acceptance: **Aug 19, 2023**
Date of Publishing: **Sep 01, 2023**