

# Prevalence, Etiological Patterns and Factors Associated with Bacteraemia Among Febrile Children with Sickle Cell Anaemia in Jinja Regional Referral Hospital, Uganda

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**Background:** Children with sickle cell anemia (SCA) are highly susceptible to bacterial infections. While studies in Sub-Saharan Africa have explored the prevalence and causes of bacteremia in SCA, no such data exist from Uganda. This study aimed to determine the prevalence, bacterial causes, and associated factors of bacteremia among febrile children with SCA at Jinja Regional Referral Hospital (JRRH).

**Methods:** We conducted a cross-sectional study among febrile children  $\leq 18$  years with confirmed SCA at JRRH. Data on socio-demographic, clinical, and laboratory variables were collected from caregivers and medical records. Blood samples were cultured using the BACTEC FX200 system and sensitivity for Kirby-Bauer disk diffusion. Descriptive statistics reported prevalence and etiology. Binary logistic regression was used to identify factors associated with bacteraemia, using SPSS v26. Statistical significance was set at  $p < 0.05$ .

**Results:** Of the 209 febrile children enrolled, 114 (54.5%) were male and 116 (55.5%) were under five years. Bacteremia was confirmed in 44 patients (21.1%). The most frequent isolate was *Staphylococcus aureus* (25/44, 56.8%), followed by *Escherichia coli* (8/44, 18.2%), *Klebsiella pneumoniae* (3/44, 6.8%), and *Haemophilus influenzae* (3/44, 6.8%). All isolates were resistant to gentamicin, ampicillin, penicillin, and ofloxacin. *S. aureus* showed good sensitivity to cloxacillin. Factors associated with bacteremia were low maternal education (aOR = 1.098; 95% CI: 1.007–1.197;  $p = 0.037$ ), tachycardia (aOR = 1.116; 95% CI: 1.027–1.213;  $p = 0.010$ ) and neutrophilia (aOR = 1.536; 95% CI: 1.363–1.731;  $p < 0.001$ ).

**Conclusion:** Bacteremia was common among febrile children with SCA, with *Staphylococcus aureus* as the leading isolate. Blood cultures should be prioritized. Ampicillin and gentamicin were ineffective, whereas cloxacillin, cefotaxime, and other antibiotics with demonstrated sensitivity are recommended as empiric alternatives.

**Keywords:** sickle cell anemia, *Staphylococcus aureus*, *Escherichia coli*, bacteremia, prevalence, Uganda

## Introduction

Sickle cell disease (SCD) is an inherited blood disorder caused by a mutation in the  $\beta$ -globin gene, a single base substitution changes from GAG to GTG, leading to the replacement of glutamic acid with valine at the sixth position of the  $\beta$ -globin chain,<sup>1</sup> causing them to become abnormally shaped like crescents, obstructing small blood vessels and reducing their lifespan.<sup>2</sup> Sickle cell anemia (SCA), the most common and severe form of sickle cell disease (SCD), occurs in individuals who are homozygous for hemoglobin S (HbSS). It is most prevalent and severe, particularly among

those of African descent in regions such as Sub-Saharan Africa, eastern Saudi Arabia, central India, and parts of the Mediterranean.<sup>1,3,4</sup>

Globally, births of babies with sickle cell disease increased by 13.7% between 2000 and 2021, reaching an estimated 515,000 in 2021.<sup>5</sup> This rise was mainly driven by population growth in high-burden regions, during the same period, the number of people living with sickle cell disease increased from approximately 5.46 million to 7.74 million, marking a 41.4% increase.<sup>5</sup>

In Uganda, around 20,000 babies are born annually with SCD, and over 80% die before their fifth birthday, often due to bacterial infections.<sup>6</sup>

Children with SCA are at increased risk of bacterial infections due to multiple immunological impairments including functional asplenia, which precedes auto-splenectomy to diminished clearance of encapsulated organisms like *Streptococcus pneumoniae* and *Haemophilus influenzae*.<sup>7</sup> These infections are a leading cause of early childhood morbidity and mortality in this population,<sup>6</sup> including pneumonia, meningitis, and septicemia.<sup>8</sup>

Despite those risk, children with SCA who present with fever are not routinely done bacterial blood cultures yet there is evidence that it can lead to invasive complications. This has resulted in unguided empirical antibiotic use, which may exacerbate the development of antimicrobial resistance in SCA children. Without data to show the burden of bacteremia in this population, the public health problem would undoubtedly remain undocumented and thus mitigation strategies could not be put in place. Studies done in other parts of Sub Saharan Africa have established the prevalence and etiology of bacteremia among children with SCA,<sup>9–11</sup> but there are no such studies in Uganda. The current study was conducted to ascertain the etiological patterns, and risk factors for bacteremia among children with SCA visiting both the outpatient clinic and the inpatient pediatric ward at Jinja Regional Referral Hospital.

## Methods and Materials

### Study Design and Setting

This was an observational, analytical cross-sectional study conducted between 21st August to 27th November 2023 at Jinja Regional Referral Hospital (JRRH) in Eastern Uganda. Data were collected from both pediatric outpatient sickle cell clinic and pediatric inpatient ward at the time of admission.

### Study Population

The study targeted children aged  $\leq 18$  years with a confirmed diagnosis of sickle cell anemia (SCA) who presented with fever (axillary temperature  $\geq 37.5^\circ\text{C}$ ). Both previously known and newly diagnosed cases were included, regardless of whether they were in a steady state or experiencing a Vaso-occlusive crisis.

### Inclusion Criteria

Febrile sickle cell anemia children ( $\leq 18$  years) with axillary temperature  $\geq 37.5^\circ\text{C}$ , and with consent/assent to participate.

### Exclusion Criteria

Children whose parents/caregivers refused blood sampling and those on therapeutic antibiotics for an illness (excluding prophylaxis).

### Sample Size Estimation

The studies objectives were to determine prevalence; etiological pattern of bacteremia and factors associated among febrile children with sickle cell anemia.

To determine the sample size the Kish Leslie formula was used:

$$n = \frac{z^2 p(1-p)}{d^2}$$

In which,  $n$  is the minimum sample size,  $Z$  is the table value for standard normal deviation, which equals 1.96 at the 95% level of significance.  $P$  = Prevalence of bacteremia in sickle cell which is 16.2% according to the study which was done at Tanzania Dodoma Regional Referral Hospital in 2021.<sup>12</sup>  $n = \frac{(1.96)^2 \cdot 0.162(1-0.162)}{(0.05)^2}$ ,  $n = \frac{3.8416 \times 0.162 \times 0.838}{0.0025}$ ,  $n = 209$

From above, our sample size was 209 participants.

## Sampling Techniques and Recruitment

Consecutive sampling was used to enroll febrile children with SCA attending either the outpatient sickle cell clinic or pediatric inpatient ward at JRRH. Recruitment was done weekly at clinic and daily at the inpatient ward. To avoid duplicate inclusion, caregivers were asked whether the child had participated the study within the last three months.

## Data Collection Tool

A structured, interviewer administered and pre-tested questionnaire was used. Pre-testing was conducted on 10 participants and was not involved in the main study. Based on feedback, there were no major changes but minor revisions were made to simplify wording and enhance clarity.

Fever was confirmed using a digital axillary thermometer (ZT-DI, Zovec Diagnostics GmbH, Germany),  $\geq 37.5^\circ\text{C}$  defined as fever.<sup>13</sup> Other clinical assessments included pulse rate, respiratory rate, and oxygen saturation. Peripheral oxygen saturation (SPO<sub>2</sub>) was considered normal above  $\geq 92\%$  and low  $< 92\%$ .<sup>14</sup> Anthropometric measurements included weight, which was recorded using a SECA baby or flat scale to the nearest 0.1 kg; height or length, measured to the nearest 0.1 cm; mid-upper arm circumference (MUAC) for children aged 6–59 months; and body mass index (BMI) and z-scores for those  $> 5$  years using WHO growth charts.

In this study, immunization status was based on Uganda's national immunization schedule. A child was considered completely immunized if they received all age-appropriate vaccines recommended for their age group, including Bacillus Calmette–Guérin (BCG), Polio Vaccine (OPV/IPV), Pentavalent vaccine (DPT-HepB-Hib), Pneumococcal Conjugate Vaccine (PCV), Rotavirus vaccine, and measles–rubella, and yellow fever vaccines. An incomplete immunization status was assigned to children who had missed any of the recommended vaccine doses for their age.<sup>15</sup> Immunization status was recorded through child health cards or caregiver recall when records were not available.

## Data Management and Analysis

Completed questionnaires were reviewed daily for accuracy and securely stored. Data entry was done using EPI Info v7 and analyzed using SPSS version 26. Descriptive statistics were used to summarize demographic and clinical characteristics. The prevalence and etiology of bacteremia were presented as frequencies and percentages. Binary logistic regression was used to identify factors associated with bacteremia. Variables with  $p < 0.2$  in bivariate analysis were included in the multivariate model, and statistical significance was considered at  $p < 0.05$ .

## Laboratory Procedure

### Blood Culture

Blood samples were collected aseptically from venipuncture site, first disinfected using 70% isopropyl alcohol and iodine, then left to dry. Using sterile gloves, 1–3 mL of blood was drawn and transferred into BD BACTEC Peds Plus/F culture bottles. Before inoculation, the needle was changed and the bottle top was cleaned with antiseptic and allowed to dry to minimize contamination. Samples were promptly transported to the laboratory.

Following the manufacturer's instructions for quality control and volume, blood was inoculated into BD BACTEC Peds Plus/F vials containing enhanced Soybean-Casein Digest broth with CO<sub>2</sub>, which supports the growth of organisms exposed to antibiotics and improves recovery of susceptible isolates. Vials were incubated in the automated BACTEC FX200 system (Becton Dickinson, Temse, Belgium).

Positive results triggered further examination by Gram stain and subculturing on solid media. If no bacteria were confirmed, the sample was labelled as negative.

Early signs of bacterial growth prompted subculturing on blood agar, MacConkey agar, and chocolate agar. Plates were incubated aerobically for blood and MacConkey agar, and anaerobically for blood and chocolate agar. After

incubation, plates were assessed for characteristic growth, followed by Gram stain and biochemical testing to confirm the organism. Suspected contaminants were assessed based on time to positivity; presence of infection signs, sepsis, and length of hospital stay before being classified as negative. Suspected contaminants are considered like single isolates of skin flora without corresponding clinical evidence.

## Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was performed using the Kirby-Bauer disk diffusion method on already prepared Mueller Hinton agar (Oxoid, Hampshire, UK) and commercially available antibiotic discs. A 0.5 McFarland standard was used to adjust the turbidity of the bacterial suspension. Colonies from pure bacterial isolates were emulsified in sterile saline and visually matched with the 0.5 McFarland standard.

A sterile swab was dipped into the suspension, excess fluid was removed, and the swab was evenly streaked over the entire surface of the Mueller Hinton agar plate. After standing at room temperature for 30 minutes to allow absorption, antibiotic discs were applied using sterile forceps. The antibiotics tested included meropenem, imipenem, nitrofurantoin, vancomycin, cloxacillin, cefotaxime, cefepime, levofloxacin, cefixime, ceftriaxone, ciprofloxacin, amikacin, chloramphenicol, ceftazidime, cotrimoxazole, cephalexin, piperacillin, clarithromycin, ceftazidime, gentamicin, ampicillin, penicillin, and ofloxacin. Plates were incubated at 37°C for 18–24 hours. The diameters of inhibition zones were measured and interpreted as Sensitive (S), Intermediate (I), or Resistant (R) based on Clinical and Laboratory Standards Institute (CLSI) criteria.<sup>16</sup>

## Full Blood Count and Blood Smear

A 2.5 mL EDTA blood sample was analyzed using a Dyne Ruby hematological analyzer (ABBOTT LABS, USA) for cell counts, Interpretation of hematologic parameters were guided by the reference ranges of Jinja Regional Referral Hospital Laboratory at the time of analysis. Blood smear (thick and thin film) was performed to rule out malaria. Positive patients for malaria were not excluded if they also met the inclusion criteria.

## Ethical Considerations

Ethical approval was obtained from Bishop Stuart University Research Ethics Committee (BSU-REC-2023-145). Administrative clearance was secured from JRRH. Written informed consent was obtained from caregivers, and assent was taken from children aged  $\geq 8$  years. All data were anonymized. COVID-19 and Ebola infection control protocols were observed throughout the study.

## Results

Between August and December 2023, 871 sickle cell patients attended JRRH. Of the 251 febrile children screened, 209 were enrolled, 29 declined consents, and 13 were on antibiotics. Among those enrolled, 44 had bacteremia, and 165 did not.

## Baseline Characteristics of the Study Participants

### Sociodemographic Characteristics

In this study that enrolled 209 children with SCA, majority were males 114 (54.5%). More than half of the participants were under five years of age 116 (55.5%), while 93 (44.5%) were aged five years and above. Most were school going 119 (56.9%). Majorities were from a rural residence 107 (51.2%). The rest of the baseline sociodemographic characteristics are shown in [Table 1](#) below.

## Previous and Current Medical History of Study Participants

A total of 147 (70.3%) of the study participants had complete immunization, while 131 (62.7%) had exclusive breastfeeding for 6 months. Majority presented with a history of cough 118 (56.5%), appetite loss 168 (80.4%) or bone pain 106 (50.7%). About 146 (70%) of the study participants were taking hydroxyurea, and 188 (90%) were taking penicillin V. The rest of the medical characteristics are shown in [Table 2](#) below.

**Table 1** Sociodemographic Characteristics of Children Aged 6 Months to 18 Years Attending the Sickle Cell Clinic at Jinja Regional Referral Hospital (N = 209)

| Characteristic            | Frequency (n) | Percentage (%) |
|---------------------------|---------------|----------------|
| <b>Age (years)</b>        |               |                |
| <5                        | 116           | 55.5           |
| 5+                        | 93            | 44.5           |
| <b>Sex</b>                |               |                |
| Male                      | 114           | 54.5           |
| Female                    | 95            | 45.5           |
| <b>School going</b>       |               |                |
| Yes                       | 119           | 56.9           |
| No                        | 90            | 43.1           |
| <b>Residence</b>          |               |                |
| Rural                     | 107           | 51.2           |
| Urban                     | 102           | 48.8           |
| <b>Care giver</b>         |               |                |
| Mother                    | 117           | 56.0           |
| Father                    | 71            | 34.0           |
| Other                     | 21            | 10.0           |
| <b>Monthly income</b>     |               |                |
| <500,000 UGX              | 159           | 76.1           |
| > 500,000+ UGX            | 50            | 23.9           |
| <b>Mother's education</b> |               |                |
| Primary and below         | 156           | 74.6           |
| Secondary and above       | 53            | 25.4           |
| <b>Father's education</b> |               |                |
| Primary and below         | 119           | 56.9           |
| Secondary and above       | 90            | 43.1           |

**Table 2** Previous and Current Medical Characteristics of Children Aged 6 Months to 18 Years Attending the Sickle Cell Clinic at Jinja Regional Referral Hospital (N = 209)

| Characteristic      | Frequency (n) | Percentage (%) |
|---------------------|---------------|----------------|
| <b>Immunization</b> |               |                |
| Complete            | 147           | 70.3           |
| Incomplete          | 54            | 25.8           |
| Never               | 8             | 3.8            |

(Continued)

**Table 2** (Continued).

| <b>Characteristic</b>             | <b>Frequency (n)</b> | <b>Percentage (%)</b> |
|-----------------------------------|----------------------|-----------------------|
| <b>Hydroxyurea use</b>            |                      |                       |
| Yes                               | 146                  | 69.9                  |
| No                                | 63                   | 30.1                  |
| <b>Penicillin V use</b>           |                      |                       |
| Yes                               | 188                  | 90.0                  |
| No                                | 21                   | 10.0                  |
| <b>EBF</b>                        |                      |                       |
| Yes                               | 131                  | 62.7                  |
| No                                | 78                   | 37.3                  |
| <b>Admission history (6/12)</b>   |                      |                       |
| Yes                               | 51                   | 24.4                  |
| No                                | 158                  | 75.6                  |
| <b>Transfusion history (6/12)</b> |                      |                       |
| Yes                               | 60                   | 28.7                  |
| No                                | 149                  | 71.3                  |
| <b>Diarrhoea</b>                  |                      |                       |
| Yes                               | 39                   | 18.7                  |
| No                                | 170                  | 81.3                  |
| <b>Vomiting</b>                   |                      |                       |
| Yes                               | 71                   | 34.0                  |
| No                                | 138                  | 66.0                  |
| <b>Cough</b>                      |                      |                       |
| Yes                               | 118                  | 56.5                  |
| No                                | 91                   | 43.5                  |
| <b>DIB</b>                        |                      |                       |
| Yes                               | 70                   | 33.5                  |
| No                                | 139                  | 66.5                  |
| <b>Chills</b>                     |                      |                       |
| Yes                               | 43                   | 20.6                  |
| No                                | 166                  | 79.4                  |
| <b>Appetite loss</b>              |                      |                       |
| Yes                               | 168                  | 80.4                  |
| No                                | 41                   | 19.6                  |

(Continued)

**Table 2** (Continued).

| Characteristic        | Frequency (n) | Percentage (%) |
|-----------------------|---------------|----------------|
| <b>Bone pain</b>      |               |                |
| Yes                   | 106           | 50.7           |
| No                    | 103           | 49.3           |
| <b>Joint Swelling</b> |               |                |
| Yes                   | 40            | 19.1           |
| No                    | 169           | 80.9           |
| <b>Pneumonia</b>      |               |                |
| Yes                   | 62            | 29.7           |
| No                    | 147           | 70.3           |

### Clinical Examination Findings

On examination, majority of the study participants had pallor 145 (69.4%), tachycardia 117 (56.0%), tachypnea 159 (76.1%) or low peripheral oxygen saturation 107 (51.2%). The rest of the examination findings are shown in [Table 3](#) below.

**Table 3** Clinical Examination Findings of Children Aged 6 Months to 18 Years Attending the Sickle Cell Clinic at Jinja Regional Referral Hospital (N = 209)

| Characteristic          | Frequency (n) | Percentage (%) |
|-------------------------|---------------|----------------|
| <b>Pallor</b>           |               |                |
| Present                 | 145           | 69.4           |
| Absent                  | 64            | 30.6           |
| <b>Ear exam</b>         |               |                |
| Normal                  | 203           | 97.1           |
| Discharging             | 6             | 2.9            |
| <b>Temperature</b>      |               |                |
| <= 38.0 °C              | 88            | 42.1           |
| 38.1+°C                 | 121           | 57.9           |
| <b>Pulse</b>            |               |                |
| Normal for age          | 92            | 44.0           |
| Tachycardia             | 117           | 56.0           |
| <b>Respiration rate</b> |               |                |
| Normal for age          | 50            | 23.9           |
| Tachypnea               | 159           | 76.1           |

(Continued)

**Table 3** (Continued).

| Characteristic | Frequency (n) | Percentage (%) |
|----------------|---------------|----------------|
| <b>SPO2</b>    |               |                |
| Low            | 107           | 51.2           |
| Normal         | 102           | 48.8           |
| <b>WLZ</b>     |               |                |
| <-2SD          | 14            | 6.7            |
| Normal         | 195           | 93.3           |
| <b>WAZ</b>     |               |                |
| <-2SD          | 19            | 9.1            |
| Normal         | 190           | 90.9           |
| <b>LAZ</b>     |               |                |
| <-2SD          | 14            | 6.7            |
| Normal         | 195           | 93.3           |

## Laboratory Findings

Majority of the study participants had severe anemia at the time of the study 116 (55.5%). The rest of the baseline laboratory findings are shown in [Table 4](#) below.

**Table 4** Laboratory Findings of Children Aged 6 Months to 18 Years Attending the Sickle Cell Clinic at Jinja Regional Referral Hospital (N = 209)

| Characteristic     | Frequency (n) | Percentage (%) |
|--------------------|---------------|----------------|
| <b>Hemoglobin</b>  |               |                |
| <7                 | 116           | 55.5           |
| 7.1+               | 93            | 44.5           |
| <b>WBC</b>         |               |                |
| Normal for age     | 132           | 63.2           |
| Leucocytosis       | 77            | 36.8           |
| <b>Lymphocytes</b> |               |                |
| Normal for age     | 162           | 77.5           |
| Lymphocytosis      | 47            | 22.5           |
| <b>Neutrophils</b> |               |                |
| Normal for age     | 128           | 61.2           |
| Neutrophilia       | 81            | 38.8           |
| <b>Platelets</b>   |               |                |
| Thrombocytopenia   | 19            | 9.1            |
| Normal             | 190           | 90.9           |

## Prevalence of Bacteremia Among Febrile Children with Sickle Cell Anemia Attending JRRH

Of the 209 children enrolled, 44 had bacterial growth on culture, a prevalence of 21.1% for bacteremia among febrile children with sickle cell anemia.

## Etiological Patterns of Bacteraemia Among Febrile Children with Sickle Cell Anemia Attending JRRH

Of the 44 patients that had bacteremia, the commonest isolate was *Staphylococcus aureus* 25 (56.8%), followed by *Escherichia coli* 8(18.2%), *Klebsiella pneumoniae* 3(6.8%), *Haemophilus influenzae* 3(6.8%), *Coagulase negative Staphylococcus* 2(4.5%), *Streptococcus pneumoniae* 2(4.5%) and *Salmonella typhi* 1(2.3%). *Staphylococcus aureus* was completely sensitive to Meropenem, Nitrofurantoin, Vancomycin and Cloxacillin. *Escherichia coli* was completely sensitive to Meropenem, Imipenem, Nitrofurantoin and Cefotaxime. *Klebsiella pneumoniae* was completely sensitive to Meropenem, Cefepime, Amikacin and chloramphenicol. *Haemophilus influenzae* was completely sensitive to Meropenem, Cefotaxime and ceftriaxone. All isolates in this study showed complete resistance to gentamicin, ampicillin penicillin, and ofloxacin, the most commonly used empirical agents. The rest of the findings regarding etiological patterns are shown in Table 5 below.

**Table 5** Etiological Patterns of Bacteremia Among Febrile Children with Sickle Cell Anemia (N = 209)

| Antibiotic     |   | <i>Staphylococcus aureus</i> 25(56.8) | <i>Escherichia coli</i> 8(18.2%) | <i>Klebsiella pneumoniae</i> 3(6.8%) | <i>Haemophilus influenzae</i> 3(6.8%) | Coagulase Negative <i>Staphylococcus</i> 2(4.5%) | <i>Streptococcus pneumoniae</i> 2(4.5%) | <i>Salmonella typhi</i> 1(2.3%) |
|----------------|---|---------------------------------------|----------------------------------|--------------------------------------|---------------------------------------|--|---|---------------------------------|
| Meropenem      | S | 100.0%                                | 100.0%                           | 100.0%                               | 100.0%                                |  |   |                                 |
| Imipenem       | S |                                       | 100.0%                           |                                      |                                       |  |   |                                 |
| Nitrofurantoin | S | 100.0%                                | 100.0%                           |                                      |                                       |  |   |                                 |
| Vancomycin     | S | 100.0%                                |                                  |                                      |                                       | 100.0%   |   |                                 |
| Cloxacillin    | S | 100.0%                                |                                  |                                      |                                       |  | 100.0%                                  |                                 |
| Cefotaxime     | S |                                       | 100.0%                           |                                      | 100.0%                                |  | 100.0%                                  |                                 |
| Cefepime       | S |                                       | 33.3%                            | 100.0%                               |                                       |  |   |                                 |
|                | I |                                       | 66.7%                            |                                      |                                       |  |   |                                 |
| Levofloxacin   | S |                                       |                                  |                                      |                                       |  | 100.0%                                  |                                 |
|                | I | 100.0%                                | 100.0%                           |                                      |                                       |  |   |                                 |
| Cefixime       | S | 40.0%                                 |                                  |                                      |                                       |  |   |                                 |
|                | I | 60.0%                                 |                                  |                                      |                                       |  |   |                                 |
| Ceftriaxone    | S |                                       | 40.0%                            |                                      | 100.0%                                |  |   |                                 |
|                | I | 10.0%                                 |                                  |                                      |                                       |  | 100.0%                                  |                                 |
|                | R | 90.0%                                 | 60.0%                            |                                      |                                       |  |   |                                 |
| Ciprofloxacin  | S | 15.4%                                 | 100.0%                           |                                      |                                       |  |   |                                 |
|                | I | 61.5%                                 |                                  | 50.0%                                |                                       |  |   |                                 |
|                | R | 23.1%                                 |                                  | 50.0%                                |                                       |  |   |                                 |
| Amikacin       | S | 38.5%                                 | 100.0%                           | 100.0%                               |                                       |  |   |                                 |

(Continued)

**Table 5** (Continued).

| Antibiotic      |   | <i>Staphylococcus aureus</i> 25(56.8) | <i>Escherichia coli</i> 8(18.2%) | <i>Klebsiella pneumoniae</i> 3(6.8%) | <i>Haemophilus influenzae</i> 3(6.8%) | Coagulase Negative <i>Staphylococcus</i> 2(4.5%) | <i>Streptococcus pneumoniae</i> 2(4.5%) | <i>Salmonella typhi</i> 1(2.3%) |
|-----------------|---|---------------------------------------|----------------------------------|--------------------------------------|---------------------------------------|--|---|---------------------------------|
|                 | I | 30.8%                                 |                                  |                                      |                                       |  |   |                                 |
|                 | R | 30.8%                                 |                                  |                                      |                                       |  |   |                                 |
| Chloramphenicol | S | 25.0%                                 |                                  | 100.0%                               |                                       | 100.0%   | 100.0%                                  | 100.0%                          |
|                 | I | 50.0%                                 |                                  |                                      |                                       |  |   |                                 |
|                 | R | 25.0%                                 | 100.0%                           |                                      |                                       |  |   |                                 |
| Cefoxitin       | S | 50.0%                                 |                                  |                                      |                                       |  |   |                                 |
|                 | R | 50.0%                                 |                                  |                                      |                                       |  |   |                                 |
| Cotrimoxazole   | S |                                       | 100.0%                           |                                      |                                       |  |   | 100.0%                          |
|                 | R |                                       |                                  |                                      | 100.0%                                |  | 100.0%                                  |                                 |
| Cephalexin      | I |                                       | 100.0%                           |                                      |                                       |  | 100.0%                                  |                                 |
| Piperacillin    | I |                                       | 100.0%                           |                                      |                                       |  |   |                                 |
| Clarithromycin  | I |                                       | 100.0%                           | 100.0%                               | 100.0%                                |  |   |                                 |
| Cefazolin       | I |                                       |                                  |                                      | 100.0%                                |  |   |                                 |
| Cefuroxime      | I | 100.0%                                |                                  |                                      |                                       |  |   | 100.0%                          |
| Erythromycin    | I | 100.0%                                |                                  |                                      |                                       |  |   |                                 |
| Clindamycin     | I | 100.0%                                |                                  |                                      |                                       |  |   |                                 |
|                 | R |                                       |                                  |                                      |                                       |  | 100.0%                                  |                                 |
| Ceftazidime     | I | 66.7%                                 |                                  |                                      |                                       |  |   |                                 |
|                 | R | 33.3%                                 |                                  | 100.0%                               |                                       |  |   |                                 |
| Gentamicin      | R | 100.0%                                | 100.0%                           | 100.0%                               | 100.0%                                | 100.0%   |   | 100.0%                          |
| Ampicillin      | R | 100.0%                                | 100.0%                           | 100.0%                               | 100.0%                                |  | 100.0%                                  | 100.0%                          |
| Penicillin      | R | 100.0%                                | 100.0%                           |                                      |                                       |  |   |                                 |
| Ofloxacin       | R |                                       | 100.0%                           |                                      |                                       |  |   |                                 |

## Factors Associated with Bacteremia Among Febrile Children with Sickle Cell Anemia Attending JRRH

Sociodemographic factors, medical factors, factors identified on clinical examination, and laboratory factors with p-values of less than 0.2 were included for analysis in multivariate logistic regression. The details of bivariate analysis are shown in Tables 6–9 below, respectively.

In the multivariate analysis, children whose mothers had a maximum of primary education had increased odds of having bacteremia (aOR = 1.098, 95% CI = 1.007–1.197, P = 0.037). Additionally, tachycardia had increased odds of bacteremia (aOR = 1.116, 95% CI = 1.027–1.213, P = 0.010), and neutrophilia had increased odds of having bacteremia (aOR=1.536, 95% CI = 1.363–1.731, P < 0.001). The details of multivariate analysis are shown in Table 10 below.

**Table 6** Bivariate Analysis of Sociodemographic Factors Associated with Bacteremia (N = 209)

| Characteristic          | No Bacteremia, N=165 | Bacteremia, N= 44 | Bivariate Analysis |              |         |
|-------------------------|----------------------|-------------------|--------------------|--------------|---------|
|                         |                      |                   | cOR                | 95% CI       | P value |
| <b>Age (years)</b>      |                      |                   |                    |              |         |
| ≤5                      | 89(42.6)             | 27(12.9)          | 1.356              | 0.687–2.676  | 0.380   |
| 5.1+                    | 76(36.4)             | 17(8.1)           | Ref                |              |         |
| <b>Sex</b>              |                      |                   |                    |              |         |
| Male                    | 89(42.6)             | 25(12.0)          | 1.124              | 0.575–2.197  | 0.733   |
| Female                  | 76(36.4)             | 19(9.1)           | Ref                |              |         |
| <b>School going</b>     |                      |                   |                    |              |         |
| Yes                     | 96(45.9)             | 23(11.0)          | 0.787              | 0.404–1.535  | 0.482   |
| No                      | 69(33.0)             | 21(10.0)          | Ref                |              |         |
| <b>Residence</b>        |                      |                   |                    |              |         |
| Rural                   | 79(37.8)             | 28(13.4)          | 1.905              | 0.959–3.783  | 0.066   |
| Urban                   | 86(41.1)             | 16(7.7)           | Ref                |              |         |
| <b>Caregiver</b>        |                      |                   |                    |              |         |
| Mother                  | 88(42.1)             | 29(13.9)          | Ref                |              |         |
| Father                  | 57(27.3)             | 14(6.7)           | 0.745              | 0.363–1.531  | 0.423   |
| Other                   | 20(9.6)              | 1(0.5)            | 0.152              | 0.019–1.181  | 0.272   |
| <b>Monthly income</b>   |                      |                   |                    |              |         |
| <500,000 UGX            | 123(58.9)            | 36(17.2)          | 1.537              | 0.662–3.568  | 0.318   |
| > 500,000+ UGX          | 42(20.1)             | 8(3.8)            | Ref                |              |         |
| <b>Education Mother</b> |                      |                   |                    |              |         |
| Primary and below       | 116(55.5)            | 40(19.1)          | 4.224              | 1.433–12.447 | 0.009   |
| Secondary plus          | 49(23.4)             | 4(1.9)            | Ref                |              |         |
| <b>Education Father</b> |                      |                   |                    |              |         |
| Primary and below       | 90(43.1)             | 29(13.9)          | 1.611              | 0.804–3.227  | 0.278   |
| Secondary plus          | 75(35.9)             | 15(7.2)           | Ref                |              |         |

**Table 7** Bivariate Analysis of Medical Factors Associated with Bacteremia (N = 209)

| Characteristic      | No Bacteremia, N=165 | Bacteremia, N= 44 | Bivariate Analysis |             |         |
|---------------------|----------------------|-------------------|--------------------|-------------|---------|
|                     |                      |                   | cOR                | 95% CI      | P value |
| <b>Immunization</b> |                      |                   |                    |             |         |
| Complete            | 112(53.6)            | 35(16.7)          |                    |             |         |
| Incomplete          | 47(22.5)             | 7(3.3)            | 0.477              | 0.198–1.149 | 0.299   |
| Never               | 6(2.9)               | 2(1.0)            | 1.067              | 0.206–5.525 | 0.939   |

(Continued)

Table 7 (Continued).

| Characteristic                    | No Bacteremia, N=165 | Bacteremia, N= 44 | Bivariate Analysis |             |         |
|-----------------------------------|----------------------|-------------------|--------------------|-------------|---------|
|                                   |                      |                   | cOR                | 95% CI      | P value |
| <b>Hydroxyurea use</b>            |                      |                   |                    |             |         |
| Yes                               | 112(53.5)            | 34(16.3)          |                    |             |         |
| No                                | 53(25.4)             | 10(4.8)           | 1.963              | 0.945–3.673 | 0.213   |
| <b>Penicillin V use</b>           |                      |                   |                    |             |         |
| Yes                               | 149 (71.2)           | 39(18.7)          |                    |             |         |
| No                                | 16(7.7)              | 5(2.4)            | 1.940              | 0.779–3.885 | 0.217   |
| <b>EBF</b>                        |                      |                   |                    |             |         |
| Yes                               | 105(50.2)            | 26(12.4)          |                    |             |         |
| No                                | 60(28.7)             | 18(8.6)           | 1.212              | 0.614–2.390 | 0.580   |
| <b>Admission history (6/12)</b>   |                      |                   |                    |             |         |
| Yes                               | 46(22.0)             | 5(2.4)            |                    |             |         |
| No                                | 119(56.9)            | 39(18.7)          | 3.015              | 1.119–8.125 | 0.029   |
| <b>Transfusion history (6/12)</b> |                      |                   |                    |             |         |
| Yes                               | 51(24.4)             | 9(4.3)            |                    |             |         |
| No                                | 114(54.5)            | 35(16.7)          | 1.740              | 0.779–3.885 | 0.277   |
| <b>Diarrhea</b>                   |                      |                   |                    |             |         |
| Yes                               | 30(14.4)             | 9(4.3)            | 1.157              | 0.503–2.660 | 0.731   |
| No                                | 135(64.6)            | 35(16.7)          |                    |             |         |
| <b>Vomiting</b>                   |                      |                   |                    |             |         |
| Yes                               | 51(24.4)             | 20(9.6)           | 1.863              | 0.945–3.673 | 0.273   |
| No                                | 114(54.5)            | 24(11.5)          |                    |             |         |
| <b>Cough</b>                      |                      |                   |                    |             |         |
| Yes                               | 93(44.5)             | 25(12.0)          | 1.019              | 0.521–1.993 | 0.957   |
| No                                | 72(34.4)             | 19(9.1)           |                    |             |         |
| <b>DIB</b>                        |                      |                   |                    |             |         |
| Yes                               | 56(26.8)             | 14(6.7)           | 0.908              | 0.446–1.850 | 0.791   |
| No                                | 109(52.2)            | 30(14.4)          |                    |             |         |
| <b>Chills</b>                     |                      |                   |                    |             |         |
| Yes                               | 35(16.7)             | 8(3.8)            | 0.825              | 0.352–1.935 | 0.659   |
| No                                | 130(62.2)            | 36(17.2)          |                    |             |         |

(Continued)

**Table 7** (Continued).

| Characteristic        | No Bacteremia, N=165 | Bacteremia, N= 44 | Bivariate Analysis |             |         |
|-----------------------|----------------------|-------------------|--------------------|-------------|---------|
|                       |                      |                   | cOR                | 95% CI      | P value |
| <b>Appetite loss</b>  |                      |                   |                    |             |         |
| Yes                   | 131(62.7)            | 37(17.7)          | 1.372              | 0.562–3.346 | 0.487   |
| No                    | 34(16.3)             | 7(3.3)            |                    |             |         |
| <b>Bone pain</b>      |                      |                   |                    |             |         |
| Yes                   | 87(41.6)             | 19(9.1)           | 0.681              | 0.349–1.332 | 0.262   |
| No                    | 78(37.3)             | 25(12.0)          |                    |             |         |
| <b>Joint Swelling</b> |                      |                   |                    |             |         |
| Yes                   | 36(17.2)             | 4(1.9)            | 1.018              | 0.120–1.068 | 0.066   |
| No                    | 129(61.7)            | 40(19.1)          |                    |             |         |
| <b>Pneumonia</b>      |                      |                   |                    |             |         |
| Yes                   | 52(24.9)             | 10(4.8)           | 0.639              | 0.294–1.391 | 0.259   |
| No                    | 113(54.1)            | 34(16.3)          |                    |             |         |

**Table 8** Bivariate Analysis of Factors Identified on Clinical Examination Associated with Bacteremia (N = 209)

| Characteristic          | No Bacteremia, N=165 | Bacteremia, N= 44 | Bivariate Analysis |              |         |
|-------------------------|----------------------|-------------------|--------------------|--------------|---------|
|                         |                      |                   | cOR                | 95% CI       | P value |
| <b>Pallor</b>           |                      |                   |                    |              |         |
| Present                 | 120(57.4)            | 25(12.0)          | 0.493              | 0.248–0.982  | 0.244   |
| Absent                  | 45(21.5)             | 19(9.1)           | Ref                |              |         |
| <b>Ear exam</b>         |                      |                   |                    |              |         |
| Normal                  | 160(76.6)            | 43(20.6)          | 1.344              | 0.153–11.807 | 0.790   |
| Discharging             | 5(2.4)               | 1(0.5)            | Ref                |              |         |
| <b>Temperature</b>      |                      |                   |                    |              |         |
| ≤38.0 °C                | 75(35.9)             | 13(6.2)           | Ref                |              |         |
| 38.1+ °C                | 90(43.1)             | 31(14.8)          | 1.987              | 0.971–4.068  | 0.040   |
| <b>Respiration rate</b> |                      |                   |                    |              |         |
| Normal for age          | 44(21.1)             | 6(2.9)            | Ref                |              |         |
| Tachypnea               | 121(57.9)            | 38(18.2)          | 2.303              | 0.911–5.823  | 0.278   |
| <b>Pulse</b>            |                      |                   |                    |              |         |
| Normal for age          | 84(40.2)             | 8(3.8)            | Ref                |              |         |
| Tachycardia             | 81(38.8)             | 36(17.2)          | 4.667              | 2.046–10.645 | <0.001  |

(Continued)

**Table 8** (Continued).

| Characteristic | No Bacteremia, N=165 | Bacteremia, N= 44 | Bivariate Analysis |             |         |
|----------------|----------------------|-------------------|--------------------|-------------|---------|
|                |                      |                   | cOR                | 95% CI      | P value |
| <b>SPO2</b>    |                      |                   |                    |             |         |
| Low            | 88(42.1)             | 19(9.1)           | 0.665              | 0.340–1.300 | 0.233   |
| Normal         | 77(36.8)             | 25(12.0)          | Ref                |             |         |
| <b>WLZ</b>     |                      |                   |                    |             |         |
| <-2SD          | 13(6.2)              | 1(0.5)            | 0.272              | 0.035–2.138 | 0.216   |
| Normal         | 152(72.7)            | 43(20.6)          | Ref                |             |         |
| <b>WAZ</b>     |                      |                   |                    |             |         |
| <-2SD          | 16(7.7)              | 3(1.4)            | 0.681              | 0.189–2.452 | 0.558   |
| Normal         | 149(71.3)            | 41(19.6)          | Ref                |             |         |
| <b>LAZ</b>     |                      |                   |                    |             |         |
| <-2SD          | 13(6.2)              | 1(0.5)            | 0.272              | 0.035–2.138 | 0.216   |
| Normal         | 152(72.7)            | 43(20.6)          | Ref                |             |         |

**Table 9** Bivariate Analysis of Laboratory Factors Associated with Bacteremia (N = 209)

| Characteristic     | No Bacteremia, N=165 | Bacteremia, N= 44 | Bivariate Analysis |              |         |
|--------------------|----------------------|-------------------|--------------------|--------------|---------|
|                    |                      |                   | cOR                | 95% CI       | P value |
| <b>Hemoglobin</b>  |                      |                   |                    |              |         |
| <7                 | 92(44.0)             | 24(11.5)          | 0.952              | 0.488–1.857  | 0.886   |
| 7.1+               | 73(34.9)             | 20(9.6)           | Ref                |              |         |
| <b>WBC</b>         |                      |                   |                    |              |         |
| Normal for age     | 122(58.4)            | 10(4.8)           | Ref                |              |         |
| Leucocytosis       | 43(20.6)             | 34(16.3)          | 9.647              | 4.395–21.172 | <0.001  |
| <b>Lymphocytes</b> |                      |                   |                    |              |         |
| Normal for age     | 130(62.2)            | 32(15.3)          | Ref                |              |         |
| Lymphocytosis      | 35(16.7)             | 12(5.7)           | 1.393              | 0.651–2.982  | 0.394   |
| <b>Neutrophils</b> |                      |                   |                    |              |         |
| Normal for age     | 127(60.8)            | 1(0.5)            | Ref                |              |         |
| Neutrophilia       | 38(18.2)             | 43(20.6)          | 10.647             | 4.395–21.172 | <0.001  |
| <b>Platelets</b>   |                      |                   |                    |              |         |
| Thrombocytopenia   | 18(8.6)              | 1(0.5)            | 0.190              | 0.025–1.464  | 0.218   |
| Normal             | 147(70.3)            | 43(20.6)          | Ref                |              |         |

**Table 10** Multivariate Analysis of Factors Associated with Bacteremia (N = 209)

| Characteristic            | Bivariate Analysis |              |         | Multivariate Analysis |             |         |
|---------------------------|--------------------|--------------|---------|-----------------------|-------------|---------|
|                           | cOR                | 95% CI       | P value | aOR                   | 95% CI      | P value |
| <b>Residence</b>          |                    |              |         |                       |             |         |
| Rural                     | 1.905              | 0.959–3.783  | 0.066   | 1.053                 | 0.968–1.146 | 0.227   |
| Urban                     | Ref                |              |         |                       |             |         |
| <b>Mother's Education</b> |                    |              |         |                       |             |         |
| <b>Primary and below</b>  | 4.224              | 1.433–12.447 | 0.009   | 1.098                 | 1.007–1.197 | 0.037   |
| Secondary plus            | Ref                |              |         |                       |             |         |
| <b>Admission history</b>  |                    |              |         |                       |             |         |
| Yes                       | Ref                |              |         |                       |             |         |
| No                        | 3.015              | 1.119–8.125  | 0.029   | 1.015                 | 0.933–1.104 | 0.725   |
| <b>Joint Swelling</b>     |                    |              |         |                       |             |         |
| Yes                       | 1.018              | 0.120–1.068  | 0.066   | 1.006                 | 0.918–1.104 | 0.894   |
| No                        | Ref                |              |         |                       |             |         |
| <b>Temperature</b>        |                    |              |         |                       |             |         |
| ≤38.0 °C                  | Ref                |              |         |                       |             |         |
| 38.1+°C                   | 1.987              | 0.971–4.068  | 0.040   | 1.043                 | 0.961–1.133 | 0.315   |
| <b>Pulse</b>              |                    |              |         |                       |             |         |
| Normal for age            | Ref                |              |         |                       |             |         |
| <b>Tachycardia</b>        | 4.667              | 2.046–10.645 | <0.001  | 1.116                 | 1.027–1.213 | 0.010   |
| <b>WBC</b>                |                    |              |         |                       |             |         |
| Normal for age            | Ref                |              |         |                       |             |         |
| Leucocytosis              | 9.647              | 4.395–21.172 | <0.001  | 1.108                 | 0.992–1.239 | 0.069   |
| <b>Neutrophils</b>        |                    |              |         |                       |             |         |
| Normal for age            | Ref                |              |         |                       |             |         |
| <b>Neutrophilia</b>       | 10.647             | 4.395–21.172 | <0.001  | 1.536                 | 1.363–1.731 | <0.001  |

## Discussion

This study was conducted at JRRH among febrile children with sickle cell anemia (SCA) revealed a 21.1% prevalence of bacteremia, which is relatively high.

A study conducted in Cameroon found a higher prevalence of 31.8% among hospitalized children with sickle cell anemia (SCA) who showed signs of infection.<sup>17</sup> Another study by Brown et al (2017) in Nigeria reported a lower prevalence of 16.8% bacteremia among febrile children with SCA, which is lower than the prevalence found in the current study. The high prevalence in our study could be attributed to the fact that only children with symptoms of febrile children were enrolled, increasing the likelihood of bacterial infection. Additionally, factors such as low maternal education and incomplete immunization may have contributed to this high prevalence.

Of the 44 patients that had bacteremia, the commonest isolate was *Staphylococcus aureus*, followed by *Escherichia coli*, *Klebsiella pneumoniae* and *Haemophilus influenzae*. Others included *Coagulase negative Staphylococcus*, *Streptococcus pneumoniae* and *Salmonella typhi*. There were varying susceptibility patterns to the different organisms as shown in Table 5, but Meropenem, Nitrofurantoin, Vancomycin and Cloxacillin had good sensitivity against *Staphylococcus aureus*. Our findings are in agreement with findings from other studies including Anderson et al and Laupland who both reported that *K. pneumoniae*, *S. aureus*, *E. coli*, and *S. pneumoniae* were the main sources of community-onset bloodstream infections among children with sickle cell disease.<sup>18,19</sup> A study conducted by Brown et al in Nigeria reported that *Klebsiella pneumoniae* and *Staphylococcus aureus* were the main causes of bacteremia in patients with SCD.<sup>10</sup> Similar findings have been reported in different African countries, including studies conducted in Nigeria, Gambia, Gabon, Tanzania, and Kenya consistently identified *Staphylococcus aureus*, *Salmonella* spp., and *Klebsiella pneumoniae* as among the most common isolates in febrile children with sickle cell disease.<sup>20–25</sup>

The most commonly used antibiotics like gentamicin, ampicillin penicillin, and ofloxacin were resistant against all the isolates in this study. The high resistance to ampicillin and gentamicin could be because all children with pneumonia and other bacterial infection are routinely treated with ampicillin and gentamicin as the first line, which could increase the possibility of resistance given that the antibiotics are at times given to children with no confirmed bacterial infection. This aligns studies with same findings from Musa et al and Mutagonda et al, where commonly used empirical antibiotics have led to rising resistance.<sup>21,24</sup>

The differences noted in the percentages of the different organisms, can be explained by the fact that bacterial isolates differ from region to region. Also, the differences in the susceptibility patterns can be explained by the difference in antibiotic use practices “antibacterial stewardship”.

This study found that children whose mothers had no education beyond the primary level had increased odds of having bacteremia. Lower maternal education has been reported in other studies to be associated with increased morbidity in children.<sup>26</sup> The explanation for this is still a topic of discussion, but many believe this association to the lower social and economic status often seen in such households, which can increase the risk of infections. For instance, low economic status may result in under nutrition as well as poor health seeking behavior which both have an increased risk of morbidity.<sup>26</sup> Tachycardia and elevated neutrophil levels were also associated with an increased odds of having bacteremia among febrile sickle cell anemia patients. Both are indicative of infection and septicemia, which helps explain their association with the presence of bacteremia.

The low prevalence of *Streptococcus pneumoniae* in our study is notable. This may reflect the impact of pneumococcal vaccination or routine use of penicillin prophylaxis in children with SCA. Further studies are needed to assess pneumococcal colonization, resistance profiles, and vaccine coverage in this setting. Routine blood culture and sensitivity testing remain underutilized in the clinical care of febrile children with SCA. Our findings highlight the value of these investigations in identifying causative organisms and guiding appropriate treatment. Increasing clinician awareness, strengthening diagnostic practices, and improving patient and caregiver education on the importance of early evaluation could enhance outcomes and support better antimicrobial stewardship in similar settings. In this study, all blood culture results were promptly shared with the treating clinicians.

## Strength and Limitations of the Study

To the best of our knowledge, this research is first research done on bacteremia among febrile children with sickle cell disease in Jinja Regional Referral Hospital and in Uganda.

This was a cross-sectional study in which conclusions about causation cannot be made.

All SCA patients who had been on antibiotics were excluded, yet these could be a significant proportion of those with bacteremia.

## Conclusion

Febrile children with sickle cell anemia should be evaluated for systemic infections through blood cultures. Additionally, the routine use of the ampicillin-gentamicin combination in the empirical treatment of suspected bacteremia should be reconsidered and replaced with a more effective regimen.

## Institutional Approval

The study received approvals from the Pediatrics Department, the Faculty of Medicine and Dentistry, and the Directorate of Postgraduate Studies at Kampala International University, as well as from the Bishop Stuart University Research Ethics Committee (BSU-REC-2023-145). Administrative clearance was granted by the Jinja Regional Referral Hospital's director. This study complies with the Declaration of Helsinki.

## Informed Consent

Informed consent was obtained from the parents or guardians of participants, with details of the study provided in both English and the local language. Children over the age of eight were asked to sign an assent form.

## Data Sharing Statement

Data can be obtained by contacting awil6263@gmail.com (corresponding author).

## Acknowledgment

The research co-authors acknowledge all the participants of the study.

## Disclosure

The authors declare that they have no conflicts of interest. We acknowledge that this manuscript was previously uploaded to Research Square as a preprint <https://www.researchsquare.com/article/rs-4997354/v1>.

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