<u>**Original Articles**</u>

Prevalence and Etiology of Bacteremia in Febrile Children with Sickle Cell Disease at a Nigeria Tertiary Hospital

Biobele Brown[1], Hannah Dada-Adegbola[2], Catherine Trippe[3] and Olufunmilayo Olopade[4]

[1] Department of Paediatrics, University College Hospital/College of Medicine, University of Ibadan, Ibadan, Nigeria.
[2] Department of Medical Microbiology, University College Hospital/College of Medicine, University of Ibadan, Ibadan, Nigeria.
[3] University of Chicago Pritzker School of Medicine, Chicago, IL, USA.
[4] Section of Hematology and Oncology, Department of Medicine, University of Chicago, Chicago, IL, USA.

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Abstract. *Background & Objectives:* **As a result of immune defects in Sickle cell disease (SCD), affected individuals are prone to infection from encapsulated bacterial pathogens like *Streptococcus Pneumoniae*. Studies on the etiological agents of bacteremia in children with SCD in Nigeria are few and have revealed a spectrum of organisms that is different from those recorded in other parts of the world.**
Aim and Objectives: **The objectives of this study were to determine the prevalence of bacteremia, etiological agents and antibiotic susceptibility pattern in febrile children with SCD attending the University College Hospital (UCH), Ibadan, Nigeria.**
Methods: **The study was cross-sectional and took place at the Department of Pediatrics of the UCH, Ibadan. Children with SCD, ages 0-17 years presenting with axillary temperature $\geq 38^{0}$C were enrolled after obtaining informed consent. History was obtained and complete physical examination performed after which blood was collected for culture and antibacterial susceptibility tests.**
Results: **A total of 116 children were studied of which 69 (59.5%) were males, 111 (95.7%) were of the Hemoglobin SS phenotype and 5 (4.3%) of the Hemoglobin SC phenotype. Bacteremia was present in 16 (13.8%) of the 116 children. Gram negative bacteria constituted 10 (62.5%) of all isolates, while the predominant isolates were *Klebsiella pneumoniae* 4, (25%) and *Staphylococcus aureus*, 4 (25%). Over 80% of the isolates were susceptible to Ceftriaxone, Amikacin and Meropenem.**
Conclusions: Klebsiella pneumoniae **and** *Staphylococcus aureus* **are the predominant causes of bacteremia in children with SCD in Ibadan, contrary to findings in western countries.**

Correspondence to: Dr. B. J. Brown. Department of Paediatrics, University College Hospital, Ibadan, Nigeria. Tel: +234 8051875510. E-mail: biosbrown@yahoo.com

Introduction. Sickle cell disease (SCD) is a genetic disorder of the hemoglobin in red cells. Globally, about 5% of the world's population carries genes responsible for hemoglobinopathies. Each year, about 300 000 infants are born with major hemoglobin disorders including more than 200 000 cases of sickle-cell anemia in Africa.[1] In Nigeria, by far the most populous country in West Africa, 24% of the population carries the mutant gene, and the prevalence of sickle-cell anemia is about 20 per 1000 births. This means that in Nigeria alone, about 150 000 children are born annually with sickle-cell anemia.[1]

As a result of immune defects in SCD, affected individuals are prone to infection from encapsulated bacterial pathogens such as *Streptococcus pneumoniae, Haemophilus influenzae*, Salmonellae and parasitic infections such as malaria, resulting in significant morbidity and mortality.[2] Few studies have reported the prevalence of bacteremia in children with sickle cell disorders in Nigeria. Okuonghae *et al.*[3] found bacteremia in 32.5 per cent of febrile children with sickle cell anemia in Benin. A recent retrospective study on hospitalized children with SCD in Ibadan revealed that 32.2 percent of them were managed for septicaemia.[4] However, some of the cases could not be confirmed by blood culture due to inability of their parents to pay for the tests. Therefore, there remains a need to confirm the prevalence of bacteremia in children with SCD prospectively to highlight the burden.

Bacterial infections have been shown to be the major cause of death in children with sickle cell disease with *Streptococcus pneumoniae* being the commonest etiological agent.[5] Consequently, neonatal diagnosis of sickle cell disorders and introduction of prophylaxis against Pneumococcus using Penicillin and vaccines have resulted in reduction in infection related deaths and improved survival of children with sickle cell disease in the United States.[6] Studies on the etiological agents of bacteremia in SCD children in Nigeria are few and have revealed a spectrum of etiological agents that is different from previously recorded in other parts of the world. Studies on etiological agents of bacteremia in Nigeria have revealed mainly Gram negative bacteria such as *Klebsiella spp* and *Salmonella spp* and in one setting *Staphylococcus aureus* as the major organisms responsible.[3,7,8] In contrast, a study from rural Kenya revealed *Streptococcus pneumoniae* as the predominant

agent responsible for septicemia in children with sickle cell disease.[9] One possible explanation to the different patterns of bacterial isolates in studies on infections in Nigeria in contrast to previous documentations in other parts of the world may be due to frequent use of antibiotics before presentation in hospital in Nigeria which could affect the result of bacterial cultures.[3,8]

Rarity in isolation of *Streptococcus pneumoniae* has made it difficult making evidence based prevention strategies against Pneumococcal infections in Nigeria.[2] In spite of this, some health centers in the country have implemented routine prophylaxis with penicillin and Pneumococcal vaccines are offered to children whose parents can afford the cost.[10] The site of the current study routinely offers pneumococcal (Pneumococcal conjugate vaccine-13 [PCV13] and Pneumococcal Polysaccharide vaccine-23 [PPSV23]) and *Haemophilus influenza* type b (Hib) vaccines to children with SCD. Never-the-less, the need to identify the common etiological agents of bacteremia in this post pneumococcal vaccination era remains pertinent in order to inform appropriate antimicrobial choices for treatment. This study was therefore carried out to determine the prevalence of bacteremia among febrile children with sickle cell disorders, the etiological agents and their antibiotic susceptibility patterns at the University College Hospital (UCH), Ibadan. This study utilized the automated bacterial culture systems (BACTEC™) which contain resins that are capable of neutralizing a wide variety of antibiotics thus allowing higher isolation rates in patients who might have commenced antibiotics before presentation;[11] this has been a major advantage over the conventional blood culture systems.

Materials and Methods. The study was cross sectional in design and took place at the children's outpatient and children's emergency ward of the University College Hospital, Ibadan. Patient enrolment took place over a period of 15 months beginning from May, 2013 during which 580 children with HbSS and HbSC were followed up at the health facility. All children with sickle cell disease (Hb SS or HbSC) presenting with fever (axillary temperature $\geq 38^0$C) were enrolled after obtaining informed consent from their parents or guardians. History was be obtained and complete physical examination performed on each child

after which blood was collected aseptically by venipuncture The needle was changed to a new one before introducing the blood collected into the broth in BACTEC bottle ped plus[TM]. Samples were processed at the Medical Microbiology laboratory of UCH for culture using BACTEC 9050 (Becton, Dickinson Diagnostic Systems, Sparks, USA) blood culture systems.[11] All the bacterial isolates were subjected, initially to direct biochemical tests for preliminary bacterial identification and antimicrobial susceptibility thereby allowing affected children to be commenced on appropriate antibiotic therapy. Further identification of bacterial isolates to the level of species was carried out by testing for enzyme systems that are characteristic of each species using the 24E Oxoid Microbact™ identification system. The antibacterial susceptibility tests were carried out using commonly employed classes of antibiotics such as penicillins, cephalosporins, aminoglycosides, quinolones, imipenem and others.[12] All microbiology tests were carried out with the standard practice as approved by Clinical and Laboratory Standard Institute (CLSI) for culture, identification and antibiotic susceptibility of bacterial isolates.[13] The disc diffusion method as described by Bauer and Kirby was employed for susceptibility testing and the report was stated as sensitive or resistant after measuring the zone of inhibition and comparing it with standard chart.[14] Control organisms included for GPC was *Staphylococcus aureus* NCTC 6571 and for Gram negative bacteria (GNB), *Escherichia coli* NCTC 35218 and *Acinetobacter baumanni* NCTC 7363. Quality control in terms of adherence to standard operating procedure (SOP) was built into each step in the isolation and identification of the bacterial also; the use of known positive and negative isolates were employed for the biochemical tests. Other relevant investigations aimed at identifying the possible foci of bacteremia including chest x-rays, culture of urine and other appropriate body fluids were done.

Blood specimen was obtained from finger prick, for preparing thick and thin films which were, air dried and stained with Giemsa and examined microscopically for malaria parasites. Results of blood culture and microscopy for malaria parasites were given to the physicians to aid the care of the children who were treated according to departmental guidelines.

Ethical Considerations: Ethical approval was obtained from the University of Ibadan/ University College Hospital Ethics Committee. Informed consent was obtained from the parents/guardians and assent from the children who were of understanding.

Data Capture and Analysis: Demographic and clinical data were obtained by one of the investigators aided by a research assistant. Data was entered on to a case record form and subsequently into a microcomputer using SPSS version 20.0. Means (and standard deviations) and medians were computed for continuous variables and comparisons made using either the T-test or Mann-Whitney U test as applicable. Categorical variables were presented as frequencies and percentages and association tested using Chi-square or Fisher's exact test as applicable. Risk factors were also assessed by computation of odd ratios and 95% confidence intervals. The susceptibility of the isolates to antibiotics in the panel was presented as frequencies. Statistical significance was set at $p < 0.05$.

Results. A total of 116 children were studied comprising 69 males (59.5%) and 47 females (40.5%). Out of these, 111 (95.7%) were of the Hemoglobin SS (Hb SS) phenotype and the remaining 5 (4.3%) of the Hemoglobin SC (Hb SC) phenotype. The 116 febrile children admitted out of the 580 children with Hb SS and HbSC followed up in the health facility in the 15 month study period yielded an incidence of 20 admissions per 100 person years.

The ages of the study patients ranged from 0.6 to 17.0 years with a mean (standard deviation) of 6.7 (4.2) years and median of 6 years. One hundred and seven (92.2%) of the study population were admitted into the hospital while the remaining 9 (7.8%) children were treated on outpatient basis. None of the study patients had been splenectomized. Blood culture was positive in 16 (13.8%) of the 116 children. In the 15 month study period, 580 children aged 0-17 years with Hb SS and Hb SC were seen in the health facility; therefore the 16 cases of bacteremia translate to an incidence of 2.2 per 100 patient years. The Gram Negative Bacteria (GNB) constituted 10 (62.5%) of all the isolates, while the common bacterial isolates were *Klebsiella pneumoniae* 4 (25%) and

Table 1. Distribution of etiological agents of bacteremia.

Organism	Frequency	Per cent
Staphylococcus aureus	4	25.0
Klebsiella pneumoniae	4	25.0
Pseudomonas aeroginosa	1	6.3
Acinetobacter baumanni	1	6.3
Stenotrophomonas maltophilia	1	6.3
Coagulase-negative *Staphylococcus*	1	6.3
Acinetobacter haemolyticus	1	6.3
Streptococcus pneumoniae	1	6.3
Salmonella pullorum	1	6.3
Salmonella subsp 2	1	6.3
Total	16	100

Staphylococcus aureus (4 (25%) as shown in **Table 1**. One case of *Streptococcus Pneumoniae* was isolated in the study and this was in a 10 year old child. This single case out of 420 children followed up at the health facility in the 0-10 year age group (in the 15 month study period) translates to 0.19 infections per 100 patient years.

Ten of the 16 cases of bacteremia were not associated with any focus of infection but the remaining 6 were. Those associated with foci of infection included 3 cases of *Klebsiella pneumoniae* infection associated with osteomyelitis, 1 case of *Pseudomonas aeruginosa* infection associated with cholecystitis and 2 cases of *Staphylococcus aureus* infections associated with Pneumonia and septic arthritis respectively.

Bacteremia was present in 11(15.9%) of the 69 boys compared with 5 (10.6%) of the 47 girls (Chi-square =661, P = 0.416). The mean (SD) age of children with bacteremia was 6.4 (4.9) years, the median was 4.5 years and the mode was 4.0 years. There was bacteremia in 8 (18.2%) of the 44 children aged less than 5 years compared with 8 (11.1%) of the 72 children aged 5 years and above (Fisher exact test p= 0.406). Thus, there was no association between bacteremia, gender and age.

The duration of fever in the study patients ranged from 1 to 10 days. The median duration of fever was 3 days in both the group with bacteremia and that without bacteremia (Mann-Whitney U test, p=0.712). The hematocrit of the children on admission ranged from 8 to 34 per cent with a mean (standard deviation= [SD]) of 21.6(5.3) percent. The mean (SD) hematocrit in the 16 patients with bacteremia was 20.4 (5.2) percent compared to 21.8 (5.3) percent in the 100 patients without bacteremia (Independent samples T test t= -0.981, p = 0.338).

Fourteen (12.1%) of the studied population had malaria parasitemia, with no bacteremia, while bacteremia was found in 16 (15.7%) of the 102 malaria negative patients. (Fisher's exact test, p =0.212). All 14 children with malaria parasitemia were given antimalarial drugs. A history of prior antibiotic use was elicited in 16 (13.8%) of the studied population, but this was not significantly associated with a reduced likelihood of a positive blood culture (**Table 2**).

Out of the 16 children who used antibiotics prior to presentation in hospital, 5 each had used Amoxicillin, and cefuroxime, 2 had used cefixime and 1each had used Amoxicillin-Clavulanate and Ampicillin. One patient had Amoxicillin-Clavulanate and Chloramphenicol serially and another had, cefuroxime and Chloramphenicol.

With regards to vaccine usage in the 116 children, 19 (16.4%) had received Hib vaccine, 10 (8.6%) had received PCV13 and 13 (11.2%) had received PPSV 23 vaccine and overall 20 (17.2%) had received at least one of any of the vaccines. None of the children who received Pneumococcal conjugate vaccine 13 (PCV 13), Pneumococcal Polysaccharide vaccine 23 (PPSV23) and *Haemophilus influenzae* type b (Hib) vaccine had a positive blood culture. Failure to use PCV 13, PPSV23 and *Haemophilus influenzae* type b Hib vaccines was each associated with a slightly increased risk of bacteremia but p-values were all greater than 0.05 (**Table 2**).

Analysis of the risk of various types of sickle cell crises with bacteremia revealed no significantly increased risk of any form of crises

Table 2. Relationship between prior antibiotic usage/ vaccination and bacteremia

Exposure factor	Exposed group		Non-exposed group Number (%)		Odd ratio	95% CI	P-value+
	N	n (%) with bacteremia	N	n (%) with bacteremia			
Prior antibiotic use	16	2 (12.5)	100	14(14.0)	0.878	0.18-4.28	1.000
Hib vaccine	19	0 (0)	97	16 (16.5)	1.20	1.10-1.30	0.070
PCV 13 vaccine	10	0 (0)	106	16 (15.1)	1.19	1.09-1.28	0.353
PPSV 23 vaccine	13	0 (0)	103	16 (15.5)	1.18	1.09-1.29	0.210
Any vaccine	20	0 (0)	96	16 (16.7)	1.2	1.1-1.3	

+ Fisher's exact test

Table 3. The contribution of bacteremia to the different forms of crises

Type of crisis	Crises		No crisis		Odd ratio	95% CI
	N	n (%) with bacteremia	N	n(%) with bacteremia		
Pain crises	66	11 (16.7)	50	5 (10)	1.8	0.6-5.6
Sequestration crises	9	1(11.1)	107	15(14.0)	0.8	0.1-6.6
Hyper-hemolytic crises	26	3(11.5)	90	13(14.4)	0.8	0.2-2.9
Aplastic crisis	2	0 (0)	114	16(14.0)	1.0	1.0-1.0

with bacteremia (**Table 3**).

Table 3 also shows the contribution of bacteremia to the different forms of crises viz: 16.7 percent of pain crises, 11.5 percent to hyper-hemolytic crises and 11.1 percent of sequestration crises.

The antimicrobial susceptibility of the isolates revealed highest susceptibility to Meropenem followed by Ceftriaxone, Amikacin and Ciprofloxacin and very low susceptibility to Amoxicillin-clavulanic acid and ceftazidime (**Table 4**).

Severe anemia defined as a hematocrit of less than 15 percent was present in 3 (18.8%) of the 16 children with bacteremia compared with 13 (13.0%) out of the 100 without bacteremia (Fisher's exact test p =0.452). Nineteen (16.4%) of the 116 children were transfused with blood, including 16 with severe anemia. Three (18.8%) of the 16 bacteremic children where transfused with blood compared to 16 (16.0%) of the 100 non-bacteremic children (Fisher's exact test p= 0.725).

Table 4. Antimicrobial susceptibility of all the isolates from blood culture.

Antimicrobial agent	Percentage sensitivity	Percentage resistance
Meropenem	100.0	0.0
Ceftriaxone	83.3	16.7
Amikacin	83.3	16.7
Ciprofloxacin	71.4	28.6
Cefuroxime	57.1	42.9
Perfloxacin	54.5	45.5
Gentamicin	50.0	50.0
Amoxycillin-Clavulanic acid	42.9	57.1
Ceftazidime	9.1	90.9

Discussion. This study has determined the incidence of bacteremia in febrile children with sickle cell disease. The 13.8% incidence observed in this study is higher than 3.4% reported in a retrospective study in London and 1.1% in another retrospective study in the United States of America.[15,16] It is however lower than 32.5% reported in Benin City, Nigeria, about two decades earlier.[3] Our finding suggests that bacteremia is more common in children with SCD in Nigeria

than in developed countries. It is tempting to assume that the lower incidence of bacteremia in London and United States may be due to routine penicillin prophylaxis and vaccinations in those settings.[15,16] However, the majority of the etiological agents of bacteremia in the present study were Gram negative organisms especially *Klebsiella pneumoniae* which corroborates two previous studies in Nigeria.[3,17] Another major etiological agent in the study was *Staphylococcus aureus* which constituted the majority of GPC isolates. Since infections by these agents are not at present vaccine-preventable, the disparity in vaccinations between developed countries and Nigeria may not account for the relatively high incidence of bacteremia in our setting. However, patients living in developed countries are most likely better nourished with better immunity and cleaner environments and with less exposure to infection than those in developing countries like Nigeria. This may explain the increased prevalence of bacteremia in this study compared to those in developed countries.

It is important to note that only 20 (17.2%) children had any of the specific vaccines for prevention of Pneumococcal and *Haemophilus influenza* type b infections. Only one isolate of *Streptococcus pneumoniae* was found and it was in an unvaccinated child. *Haemophilus influenzae* type b was not isolated in the study. The predominant isolates were *Klebsiella pneumoniae* and *Staphylococcus aureus* which is in keeping with previous studies and further confirms that both organisms play significant roles in bacteremia among febrile individuals with sickle cell disease in Nigeria.[3,17] The rarity of *Streptococcus pneumoniae* infection in this study is contrary to findings in developed countries before the institution of routine penicillin prophylaxis and vaccination and also discordant with what was reported in Kenya.[5,9] The 0.19 infection per 100 person-years incidence of invasive pneumococcal disease (IPD) in children aged 10 years or less in the present study is low compared to 1.7 infections

per 100 person -years in a US based study on children of a similar age group.[18] The low incidence may be contributed to by the small proportion of children aged 2 years or less in the cohort since most cases, sometime, as much as 79 % of IPDs may occur in the first 2 years of life[19] but only 15 % of children followed up in our facility are in that age group due to late diagnosis. The low incidence is however in agreement with findings in previous studies in Nigeria and a study in Uganda.[3,8,20] A study in Tanzania also revealed a predominance of *Staphylococcus aureus* and rarity of *Streptococcus pneumoniae*.[21] Reasons that have been attributed to the low incidence of Pneumococcal infections in some African countries include greater difficulty in isolating fastidious organisms like Pneumococcus compared with organisms like *Staphylococcus aureus* and the possibility of unregulated antibiotic usage in these countries.[9,22] It is possible that use of antibiotics purchased across the counter for febrile illnesses eliminate some organisms including Pneumococci such that affected children rarely present in hospital. Consequently, only infections not cleared by such antibiotics present in the hospital. Although only 13.8 percent of the study population had used antibiotics, the drugs mainly used were penicillins or penicillin derivatives and cephalosporins to which *Streptococcus pneumoniae* is usually susceptible. It is however not clear if this degree of pre-hospital antibiotic usage reflects that of the rest of the sickle cell disease population and also if it is sufficient to account for the low rate of isolation of *Streptococcus pneumoniae*. In spite of the various aforementioned postulations, the consistent rarity of *Streptococcus pneumoniae* and predominance of *Klebsiella* and/or *Staphylococcus aureus* in multiple African countries, may be true representations of common organisms in tropical African countries.

Since the utility of Pneumococcal vaccines in the study population was low, vaccine usage may not completely account for the low rate of Pneumococcal infection. The slightly increased risk of bacteremia in children who did not use any of the stipulated vaccines needs to be interpreted with caution. Although the 95 % confidence intervals did not include the null value (1.0), the p values were all greater than 0.05 and the amount of increased risk reflected by the odd ratios were minimal. This implies that protection from infections caused by organisms (*Streptococcus Pneumoniae* and *Haemophilus influenza* type b) covered by the stipulated vaccines has little if any contribution to the relative reduction (albeit statistically insignificant) of overall incidence of bacteremia in the vaccinated group. This highlights the insignificant contribution of *Streptococcus Pneumoniae* and *Haemophilus influenza* type b infection to bacteremia in the study population.

Although this study was not focused primarily on osteomyelitis, the association with 3 cases of Klebsiella infection suggests an important role of this organism in bone infections in sickle cell anemia in this setting and therefore the need to bear this in mind when prescribing antibiotics especially when first line drugs have failed.

In spite of conflicting data on the incidence of pneumococcal infections in Africa and consequent doubts on the need for routine vaccinations, some countries in the continent have initiated routine pneumococcal vaccinations against the backdrop of evidence of its benefits observed in other parts of the world.[23] Emphasis should therefore be on the knowledge of prevalent isolates of bacteremia and their antimicrobial susceptibility patterns to guide the choice of first line antibiotics in febrile children with sickle cell disease. A previous study on adults with SCD in the same hospital as the present study reported a similar pattern of etiological agents but reported Ceftazidime to be the most effective antibacterial agent to which 93% of GNB and 82.5% of Gram positive bacteria were susceptible,[17] while the current study revealed a very low susceptibility to Ceftazidime. The reduced susceptibility to ceftazidime is in keeping with development of resistance over the last 20 years. The top four antibiotics to which the isolates were most susceptible in this study were Meropenem, Ceftriaxone, Amikacin and Ciprofloxacin. A hundred percent susceptibility observed with Meropenem showed the need to restrict the use of Carbapenems in order to reduce the development of multidrug resistance.[24] We therefore recommend the use of Ceftriaxone and Amikacin as first line antibiotics after collection of blood culture specimen in this setting. Meropenem may therefore be a reserve drug that is employed in multi-drug resistant cases and strictly after a susceptibility report to justify its administration. This should also be incorporated into the antibiotic

policy of the hospital in keeping with antibiotic drug stewardship guidelines.

In the present study, there was no significant difference in the hematocrit on admission of children with bacteremia compared with those without bacteremia. This is at variance with findings by Makani *et al.*[21] in Tanzania where children with bacteremia were more likely to have a lower hemoglobin concentration compared with those without bacteremia. The reason for this difference may be due to differences in the cohorts in the two studies. Whilst the present study was only on febrile children who are likely to have infections, that from Tanzania was from all SCD admissions irrespective of the diagnosis which is therefore likely to include non-infective cases. The co-morbidities in the non-bacteremic cases in both studies are therefore likely to be different.

The findings in this study of infections associated with crisis is keeping with the recognized role of infections as precipitants of crisis in SCD. During infection, changes occur at a cellular level, which predispose to crises. Levels of circulating leukocytes and inflammatory cytokines increase, with elevated expression of adhesion molecules on both the vascular endothelium and leukocytes themselves. Leucocytes attracted to sites of inflammation also produce cytotoxic proteins such as proteases, collagenase, and elastase and generate reactive O_2 radicals, which cause oxidative damage. This promotes further endothelial activation and cell adhesion.[25] Cell adhesion subsequently leads to microvascular occlusion and sickling. In addition, fever with insensible water loss, reduced oral fluid intake, diarrhea, and vomiting in infections may contribute to dehydration which increases the risk of sickling.[26]

Conclusions. This study has revealed a 13.8 percent incidence of bacteremia in febrile children with sickle cell disease, a figure that appears higher than observed in developed countries. The study has also highlighted the rarity of *Streptococcus pneumoniae* in African children in line with a number of studies in Africa, adding to the debate of the need for Pneumococcal vaccines in children with sickle cell disease in such settings. Incidentally, following the implementation of routine Pneumococcal vaccinations in some African countries, the actual role played by Pneumococcal infection may never be known. Nevertheless, the study has revealed that like some other African countries, the major causes of bacteremia are *Klebsiella pneumoniae* and *Staphylococcus aureus*. The results of antibiotic susceptibility to the common organisms would serve as a guide to first line antimicrobial prescription in suspected cases of bacteremia.

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