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Prevalence and pattern of bacteraemia among HIV-infected under-five children in a tertiary hospital in Kano, Nigeria

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Abstract*: Background:* Bacteraemia is an invasive bacterial disease of childhood that is associated with serious complications and high mortality especially in immunocomprised HIV infected children.
Aim: To determine the prevalence and pattern of bacteraemia among HIV-infected Under-five children.
Design: It was a prospective cross-sectional study
Subjects and Methods: One hundred and thirty four febrile HIV-infected children were recruited from the outpatient departments and emergency room of a tertiary hospital to determine the presence of bacteraemia, the etiologic agent and antibiotics susceptibility. An automated (BACTEC) incubator was used to detect bacteraemia, subcultures were done and identification and antibiotic susceptibility tests were done using standard laboratory procedures. Socio-demographic and clinical data were obtained using a proforma and data analysis was done using SPSS version 17.0 for windows.
Results: The prevalence of bacteraemia in HIV-infected children was 14.2% (19/134). *Salmonella typhi* and *Staphylococcus aureus* were the predominant isolates, each accounting for 21% of all cases of bacteraemia. Most (81.3%) of the subjects were on HAART and its use had no effect on rate of bacteraemia. Fourteen (73.7%) and 12(63.2%) of the isolates were sensitive to ciprofloxacin and ceftriaxone respectively. Sensitivities to ampicillin, cloxacillin and co-trimoxazole were 0.0%, 5.3% and 5.3% respectively.
Conclusion: Bacteraemia is a significant health problem among HIV-infected under-five children despite the high rate of HAART use. Treatment adherence should be strengthened among this population. There is need for improvement in personal and food hygiene, environmental sanitation and possibly introducing typhoid vaccine among under-five HIV-infected children.

Keywords: bacteraemia, under-five, human immunodeficiency virus/acquired immune deficiency syndrome, prevalence, highly active antiretroviral therapy.

Introduction

Seventy one percent of world's HIV-infected children live in Sub-Saharan Africa.[1] Nigeria accounts for an estimated 10% of global burden of HIV/AIDS and 30% of the burden of mother-to-child transmission of HIV with the national HIV prevalence rate of 3.4%.[2,3] Over 440,000 Nigerian children under the age of 15 years are living with the infection and three out of every 100 deaths in children are due to HIV/AIDS directly or indirectly.[2,4]

Bacteraemia is the presence of viable bacteria in the circulating blood.[5] This may or may not be symptomatic depending on the presence of an underlying turbulent cardiac flow or immunosuppression as in HIV infection. A form of clinical bacteraemia associated with fever but no evidence of sepsis or clear focus of infection is termed "occult bacteraemia".[6] In this report, we shall use the term "bacteraemia" to mean all clinically significant forms.

In the HIV-infected, bacteraemia is a serious condition that often persists and could lead to potentially lethal diseases including pneumonia, septic arthritis, osteomyelitis, meningitis and severe sepsis.[7] Factors such as abnormalities in humoral and cell-mediated immunity, phagocytic cell dysfunction and skin and mucous mem-

brane defects all contribute to higher risk of bacteraemia in them.[8] Bacterial infections are responsible for the immediate cause of death of up to 30% of patients with HIV infection.[9]

Unfortunately, 630,000 African children are receiving Anti-retroviral Therapy (ART) which corresponds to only 22% of those that are eligible.[10] In Nigeria, the situation is even more distressing as only 15% of the eligible 92,200 Nigerian HIV-infected children have access to this life-saving treatment modality.[2]

There is a paucity of data on bacteraemia in HIV-infected children particularly in the northern part of the country. More so, results from few studies from other parts of the country such as Benin[11] may not be applicable to patients in our locality. This study was carried out to determine the prevalence and pattern of bacteraemia in HIV-infected children. It is hoped that results of this study would provide the basis for cost-effective interventions such as chemoprophylaxis, vaccinations and rational use of antibiotics that will improve the management and outcome of children with HIV/AIDS.

Subjects and Methods

Study design

The study was a hospital-based prospective cross-sectional study conducted between August 2014 and June 2015.

Study population

The study population included children aged between 6 weeks and 60 months, confirmed to have HIV infection presenting on follow up to the Pediatric Infectious Diseases Clinic (PIDC) and the Emergency Pediatrics Unit (EPU).

Inclusion criteria

HIV-infected children aged between 6 weeks and 60 months, on follow up at the PIDC and EPU during the study period. Those who were either febrile or hypothermic at presentation and whose parents/caregivers consented to the study.

Exclusion criteria

Those who had antibiotics (other than co-trimoxazole which is routine in under-five HIV-infected children) within one week prior to enrolment.

Ethical approval

Ethical approval for the study was obtained from the Research and Ethics Committee (REC) of the hospital.

A written informed consent to enroll the patient into the study was obtained from the parent(s) or the accompanying caregiver(s) of each child.

Sampling/data collection

By serial recruitment, every eligible HIV-infected child who met the inclusion criteria was recruited from the PIDC or EPU. Diagnosis of HIV infection was based on the Nigerian national protocol.[4]

During routine clinic visit and emergency room consultation, eligible participants were identified, proforma administered and blood samples were obtained for blood culture and blood counts. A complete physical examination was also carried out on each child.

Subjects were classified based on the history, clinical examination findings and most recently documented CD4 count into the appropriate WHO clinical and immunological stages. The Partec Cyflow counter serial number 050117117 was used for the estimation of CD4 count and percentages were calculated as a fraction of the Total Lymphocyte Count (TLC) obtained from full blood count of the same sample. The most recent CD4 percentages obtained during infection free period were used to classify subjects into different immunologic categories using the revised WHO staging of 2007.

Sample collection

In each case, the procedure was explained to the parent/caregiver. The site thoroughly cleaned, with 70% isopropyl alcohol solution and tourniquet applied, followed by povidone iodine solution that was applied in a circular pattern and then allowed to dry. Two to three milliliters (2-3ml) of blood was obtained following a sterile procedure by inserting an appropriate-sized vacutainer needle into an antecubital vein in the arm or any other site deemed appropriate with the opposite end puncturing into the vial for direct inoculation. Prior to the inoculation, the flip-off cap of the commercially produced vials containing BD BACTEC ™ Peds Plus ™ media was wiped with alcohol swab and allowed to dry. An additional 2mls of blood was put in an EDTA bottle for blood counts which served as an initial markers of infection pending the availability of culture results.

Laboratory methods

Inoculated blood culture vials were delivered to the laboratory within one hour of collection for placement in the incubator. Samples were incubated in the automated BACTEC 9050 blood-culture system (Becton Dickinson, Temse, Belgium) for a maximum of five days. Whenever there was a positive signal from the incubator (usually within 48 hours), an aliquot was obtained from the vial with a sterile syringe and needle and further examined by Gram stain and sub-cultured onto appropriate solid media (blood, chocolate and MacConkey agars) for 48 hours. Vials with no signals after five days of incubation in the BACTEC system were checked by Gram stain and sub-cultured onto solid media for the same duration of 48 hours prior to discarding as negative. Blood cultures were considered positive if a definite non-contaminant pathogen was isolated after a maximum of seven days.

For bacterial identification, all positive blood cultures were examined directly by Gram stain microscopy and subcultured on standard media plates. Identification of the organisms was obtained by biochemical and serological tests. Susceptibility to ampicillin, amoxicillin-clavulanate, cefuroxime, ceftazidime, ceftriaxone, co-trimoxazole, ciprofloxacin, cloxacillin, gentamicin, oxacillin and ofloxacin were tested using the Kirby-Bauer disc diffusion method. Preliminary results were made available to the managing physicians within 48 hours and the final results after subculture and sensitivity in 7-9 days.

Data analysis

Statistical analysis was conducted using the statistical software package, SPSS version 17.0 (Chicago, IL, USA). Data were presented using frequency tables and cross-tabulations. Quantitative variables were summarized using the mean, median, range, interquartile range and standard deviation while qualitative variables were summarized using frequencies and percentages. Chi square (χ^2) test was used to determine significance of association between age and prevalence of bacteraemia and Odds ratio (OR) for association between use of HAART and prevalence of bacteraemia. Confidence level was set at 95% and a p-value of < 0.05 was considered significant.

Results

A total of 134 febrile HIV-infected were recruited with a mean age (SD) of 25(16.6) months. There were 80 (59.7%) males and 54(40.3%) females and the male-to-female ratio was 1.5:1. Forty five (33.6%) of the subjects were infants and 108(80.6%) were of the Hausa/ Fulani ethnicity. Half (50%) of them were from the lower socio-economic class (Table 1).
One hundred and nine (81.3%) subjects were on HAART and the highest proportion (32/34) of those on HAART was among the 36-59 month age group (Fig 1).

Fig 1: Proportion of HIV-infected group on HAART according to age groups

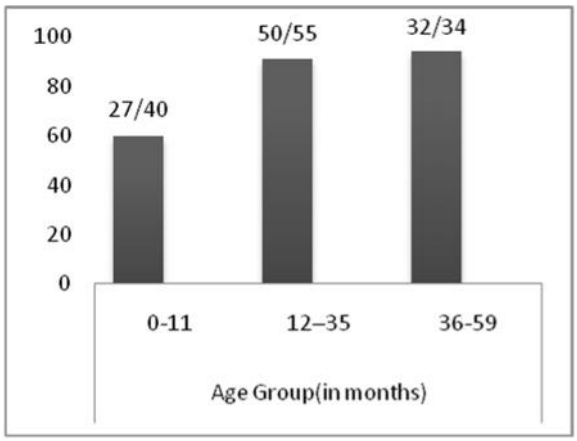

Table 1: Socio-demographic characteristics of the subjects

Variable	Frequency(%)
Age categories (months)	
0-11	45(33.6)
12-35	55(41.0)
36-60	34(25.4)
Mean (SD)	25(16.6)
Gender	
Male	80(59.7)
Female	54(40.3)
Ethnic Group	
Hausa/Fulani	108(80.6)
Yoruba	5(3.7)
Igbo	10(7.5)
Others	11(8.2)
Socio-Economic Class	
Lower	67(50.0)
Middle	52(38.8)
Upper	15(11.2)
Maternal Education	
Tertiary	6(4.5)
Secondary	15(11.2)
Primary	45(33.6)
No formal education	68(50.7)

The overall prevalence of bacteraemia was 14.2% (19/134). The prevalence was 15.6%, 12.7% and 14.7% for the 0-11months, 12-35months and 36-59months age groups respectively. There was no statistically significant association between age and bacteraemia (Table 2).
The predominant organisms responsible for bacteremia were *Salmonella typhi* and *Staphylococcus aureus*, each accounting for 4/19(21%) respectively. *Streptococcus pneumoniae* was the second commonest isolate accounting for 3 /19(15.8%)(Table 3).

Table 2: Prevalence of bacteraemia according to age groups among HIV-infected children

	Bacteremia	
Age Group(mo)	Positive	Negative
0-11	7(15.6)	38(84.4)
12-35	7(12.7)	48(87.3)
36-59	5(14.7)	29(85.3)
Total	19(14.2)	115(85.8)

χ^2=0.17, df=2, p-value = 0.92

There was no statistically significant difference in the prevalence of bacteraemia between those on HAART and those that were ARV-naïve (Table 4).
Fourteen(73.7%) of the isolates were susceptible to ciprofloxacin while 12(63.2%) were susceptible to ceftriaxone. The only NTS isolated was sensitive to co-trimoxazole, ciprofloxacin and amoxicillin-clavulanate. Susceptibility to co-trimoxazole was 1(5.3%) and the overall sensitivity was lowest for ampicillin(0.0%) and oxacillin(0.0%)(Table 5).

Table 3: Etiologic agents of bacteraemia in subjects

Organism	S typhi	S aureus	S. pneumo	Other K. spp	Kleb pneumo	HIb	NTS	E.coli	Proteus spp	CoNS	Total (%)
No of isolates (%)	4 (21.0)	4 (21.0)	3 (15.8)	2 (10.5)	1 (5.2)	1 (5.3)	1 (5.3)	1 (5.3)	1 (5.3)	1 (5.3)	19 (100.0)

Organisms: S. typhi-Salmonella typhi, S. aureus-Staphylococcus aureus, S.pneumoniae - Streptococcus pneumonia, K. pneumo – Klebsiella pneumoniae, Hib –Haemophilus influenza type b, NTS-Non-typhoidal Salmonella, K. spp – Klebsiella species, E. coli- Escherichia coli, Proteus spp – Proteus species CoNS- Coagulase-Negative Staphylococcus.

Table 5: Antibiotic sensitivity pattern by isolates in HIV-infected subjects

Isolates	No.	CIP	OFL	CFZ	AMP	CXO	CFU	GEN	AUG	CLO	OXA	COT
S. typhi	4	3	-	-	-	3	3	2	2	-	-	-
S.aureus	4	4	-	1	-	3	-	2	-	1	-	-
S. Pneumo	3	-	-	3	-	2	1	-	1	-	-	-
Other Kleb sp	2	2	-	2	-	-	-	1	-	-	-	-
Kleb. pneumo	1	1	-	-	-	-	-	1	-	-	-	-
Hib	1	-	-	1	-	1	1	-	1	-	-	-
NTS	1	1	-	-	-	-	-	-	1	-	-	1
E. coli	1	1	-	-	-	1	-	-	1	-	-	-
Proteus spp	1	1	1	-	-	1	-	-	-	-	-	-
CoNS	1	1	-	-	-	1	-	1	-	-	-	-
Total	19(100.0)	14(73.7)	1(5.3)	7(36.8)	-(0.0)	12(63.2)	5(26.3)	7(36.8)	6(31.6)	1(5.3)	0(0.0)	1(5.3)

Isolates:
S. typhi-*Salmonella typhi*, S. aureus-*Staphylococcus aureus*, S.pneumo - *Streptococcus pneumoniae*, Kleb. pneumo – *Klebsiella pneumoniae*, Hib –*Haemophilus influenza*e, NTS-Non-typhoidal Salmonella, Kleb. spp – *Klebsiella species*, E. coli- *Escherichia coli*, Proteus spp – *Proteus species*, CoNS- Coagulase-Negative Staphylococcus.
Antibiotics:CIP- Ciprofloxacin, OFL- Ofloxacin ,CFZ- Ceftazidime, AMP- Ampicillin, CXO- Ceftriaxone, CFU- Cefuroxime, GEN- Gentamicin, AUG- Amoxi-clavulanate, CLO- Cloxacillin, OXA-Oxacillin, COT- Co-trimoxazole.

Table 4: Relationship between the use of HAART and prevalence of bacteraemia

HAART	Bacteraemia		
	Positive (%)	Negative(%)	Total (%)
Yes	15(13.8)	94(86.2)	109(100.0)
No	4(16.0)	21(84.0)	25(100.0)
Total	19(14.2)	115(85.8)	134(100.0)

OR[95% CI]=0.84[0.25, 2.79]

Discussion

In this study, the prevalence of bacteraemia in HIV-infected under-five children was 14.2%. This is similar to the report by Madhi et al.[12] with high rate of bacteraemia in HIV infected children of comparable age group. The prevalence from our study is also similar to that in the Anti Retroviral Research of Watoto (ARROW) study (14.5%)[13] and also the 15.5% found in a study at the Kwa-Zulu Natal hospital in South Africa.[14] However, prevalence observed by Imade and colleague[11] in Benin was much higher(37.1%). This difference may be due to the fact that most of the subjects in our study were on HAART and may have been able to reconstitute their immune system thereby having a lower predisposition to opportunistic infections. In addition, we found a very low rate of bacteraemia due to Coagulase-Negative Staphylococcus (CoNS) which is a notable contaminant. This might have significantly reduced the rate of falsely positive cultures associated with other methods of culture that were used in many of the other studies that reported higher prevalence.

The prevalence of bacteraemia was not related to age among the HIV-infected subjects. This is not consistent with the fact that the immune system is normally most naïve at birth and develops over time. Our finding may be explained by the presence of HIV infection which is likely to have distorted the trend.[12]

A previous HIV study suggested that apart from the higher burden of bacteraemia in sub-Saharan Africa, the spectrum of aetiologic agents differ from those in developed world.[15] Such differences may also be seen within developing countries. An increase in bacteraemia due to non-typhoidal Salmonella (NTS) and Mycobacteria species was observed among HIV-infected individuals in a 2010 study in Uganda,[16] but we observed that *Salmonella typhi* and *Staphylococcus aureus* are the most predominant causes of bacteraemia in HIV-infected in our population. The present study was among under-five children with poorer hygiene practices (compared to adults) while the Ugandan study was among older population in addition to the fact that aerobic culture media used in our study is not suitable for isolating Mycobacteria. The finding of *Salmonella typhi* as a common isolate may be explained by the low level of water and food hygiene that characterize most poor and developing societies like Nigeria[17]. However, this finding is in contrast to Tanzanian studies that reported and postulated

low risk for *Salmonella typhi* among HIV-infected population.[18,19] Understandably, *Staphylococcus aureus* is a ubiquitous organism that commonly colonizes the skin and nostril of most individuals regardless of the immune status, they become pathogenic when they find their way into deeper body structures which is easier in HIV infection as a result of defective mucosal barriers.[20] Our findings agree with reports of Imade *et al.*[11] in Benin Nigeria and Nchabeleng *et al*.[14] in Kwa-Zulu Natal, South Africa where *Staphylococcus aureus* was found to be the commonest isolate.

Apart from the Benin study where they found a high rate of CoNS in the ARV-naïve HIV-infected subjects, CoNS is not a prominent cause of bacteraemia in HIV-infected children.[13,14] We found only one case (5.3%) of CoNS infection in this study and that was detected in a subject with advanced immunosuppression. This may be because they are mainly opportunistic bacteria that are expected to be more frequent in the immunosuppressed and those with prosthetic devices and indwelling catheters.[21] In addition, the automated culture system is associated a low rate of contamination by organisms such as CoNS.

Even though some studies have report that Mycobacteria plays notable role in bacteraemia among HIV infected children, our study cannot corroborate or refute their findings since we only utilized aerobic media which is incapable of isolating Mycobacteria

The use of HAART significantly reduces the progression of paediatric HIV/AIDS.[22,23] Over four-fifths (81%) of our HIV-infected subjects were on HAART which may be another reason for the lower rate of bacteraemia when compared to findings of Imade et al and Madhi et al. Hospital-based studies in Africa prior to the advent of HAART showed that bacteraemia was three times more frequent among the HIV-infected than in the HIV-uninfected people and five times more likely to cause death.[24-26]

The isolates were sensitivity to ciprofloxacin and ceftazidime and highly resistant to co-trimoxazole. There was significant sensitivity of *Salmonella* to ciprofloxacin but it was not as susceptible to amoxicillin-clavulanate and gentamicin as observed among a Thai population of HIV-infected subjects.[27] Until recently, ciprofloxacin had not been recommended for use in children due to concerns about its musculoskeletal adverse effects.[28] Recent studies have shown that these are mild, transient and reversible.[29] This concern over the years may have relatively preserved ciprofloxacin and other fluoroquinolones (like ofloxacin) thereby retaining their efficacy and preventing the development of resistance.

Ampicillin resistance was high in our study. Similarly, in separate studies by Imade et al.[11] and Madhi et al.[12] this was the case. Furthermore, nearly all the isolates were resistant to co-trimoxazole just as Madhi et al.[12] reported in Soweto. This is largely attributable to its routine use in the HIV group as prophylaxis against opportunistic infections like Pneumocyctis jiroveci pneumonia (PCP), toxoplasmosis and malaria.

Conclusion

Bacteraemia is an important cause of morbidity and mortality among under-five HIV-infected children. *Salmonella typhi* and *Staphylococcus aureus* are important etiologic agents in children with HIV infection. The use of the highly active antiretroviral therapy is expected to reduces the rate of bacteraemia but compliance is more important. We recommend the use of ciprofloxacin or ceftriaxone as the empiric first line antibiotics in any suspected case of bacteraemia in under-five HIV-infected children. We also suggest the need to improve food and water hygiene and, in the short-term, consider introduction of mass vaccination against *Salmonella typhi* to help reduce the rate of *Salmonella typhi* bacteremia in HIV-infected children. Ampicillin, oxacillin, cloxacillin and co-trimoxazole as empiric first-line antibiotics in the management of suspected bacteraemia should be discouraged.

Limitation

The culture media used in this study is not sensitive for detecting mycobacteria and anaerobic bacteria which may play some role in significant bacteraemia

Authors' Contribution
Adisa AK and Hassan-Hanga F conceptualized the study, Adisa AK recruited the subjects and analyzed the data.
Oyelami OA reviewed the concept and edited the manuscript.
Conflict of Interest: None
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