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Predictors of Bacterial Co-Infection and Outcome in Children with Severe Malaria in Ilorin, Nigeria

Prédicteurs de la Co-Infection Bactérienne et des Résultats Chez les Enfants Paludisme Grave à Ilorin, Nigéria

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ABSTRACT

BACKGROUND: Severe malaria is a significant cause of morbidity and mortality in Nigeria and concomitant bacteraemia may potentially worsen clinical outcomes. (Duration of admission, Mortality, Fever clearance time and Coma recovery time)

OBJECTIVES: This study aimed at identifying the proportion of children with severe malaria who had concomitant bacteraemia, the pathogens implicated and their drug sensitivity pattern, predictors of bacterial co-infection and its effect on treatment outcome.

METHODS: This was a hospital-based cross-sectional study at the Emergency Paediatric Unit of the University of Ilorin Teaching Hospital, Nigeria. The subjects were children aged 6 months to 14 years with severe malaria and microscopy confirmed parasitemia at admission. All subjects had blood culture samples drawn at admission for identification of bacterial isolates. Relevant clinical and laboratory parameters were recorded on case proformas.

RESULTS: A total of 944 children were admitted into the Emergency Paediatric Unit during the study period with 176 (18.6%) managed for severe malaria. Of the 176 children with severe malaria, 41 (23.3%) had concomitant bacteraemia. Gram positive bacteria were the most common (70.7%) isolates with *Staphylococcus aureus* being the most predominant (65.9%). The bacterial isolates were mostly sensitive to Ciprofloxacin. Children with concomitant bacteraemia had a longer duration of admission ($p = 0.028$) and longer fever clearance time ($p = 0.015$). Increasing duration of coma before presentation was the single independent predictor of bacteraemia ($p = 0.010$).

CONCLUSION: Severe malaria constituted a significant cause of admissions in UITH with approximately a fourth of the subjects having bacterial co-infection and this was associated with a worse prognosis (longer duration of admission and fever clearance time). Increased duration of coma prior to admission was the only predictor of the presence of bacteraemia in children with severe malaria. This highlights the importance of investigating for concomitant bacteraemia, especially in children presenting with coma. WAJM 2021; 38(3): 274–281.

ABSTRAIT

CONTEXTE: Le paludisme grave est une cause importante de morbidité et mortalité au Nigéria et bactériémie concomitante peut potentiellement aggraver les résultats cliniques. (Durée de admission, mortalité, temps d'élimination de la fièvre et rétablissement dans le coma temps)

OBJECTIFS: Cette étude visait à identifier la proportion de les enfants atteints de paludisme sévère qui ont eu une bactériémie concomitante, les agents pathogènes impliqués et leur schéma de sensibilité aux médicaments, prédicteurs de la co-infection bactérienne et de son effet sur le traitement résultat.

MÉTHODES: Il s'agissait d'une étude transversale en milieu hospitalier l'Unité de pédiatrie d'urgence de l'Université d'Ilorin Hôpital universitaire, Nigéria. Les sujets étaient des enfants de 6 ans mois à 14 ans avec paludisme sévère et microscopie confirmée parasitemie à l'admission. Tous les sujets avaient des échantillons d'hémoculture prélevé à l'admission pour l'identification des isolats bactériens. Les paramètres cliniques et de laboratoire pertinents ont été enregistrés sur formulaires de cas.

RÉSULTATS: Au total, 944 enfants ont été admis dans le Unité pédiatrique d'urgence pendant la période d'étude avec 176 (18,6%) pris en charge pour le paludisme grave. Sur les 176 enfants avec paludisme sévère, 41 (23,3%) avaient une bactériémie concomitante. Gramme les bactéries positives étaient les isolats les plus courants (70,7%) avec *Staphylococcus aureus* étant le plus prédominant (65,9%). Les isolats bactériens étaient pour la plupart sensibles à la ciprofloxacine. Les enfants atteints de bactériémie concomitante avaient une durée plus longue d'admission ($p = 0,028$) et un temps d'élimination de la fièvre plus long ($p = 0,015$).

L'augmentation de la durée du coma avant la présentation était la seule prédicteur indépendant de bactériémie ($p = 0,010$).

CONCLUSION: Le paludisme sévère constituait une cause importante des admissions à l'UITH avec environ un quart des sujets avoir une co-infection bactérienne et cela a été associé à une pronostic (durée d'admission plus longue et élimination de la fièvre temps). L'augmentation de la durée du coma avant l'admission était la seul prédicteur de la présence de bactériémie chez les enfants paludisme grave. Cela souligne l'importance d'enquêter sur en cas de bactériémie concomitante, en particulier chez les enfants présentant avec coma. WAJM 2021; 38(3): 274–281.

Keywords: Bacteraemia, Severe malaria, Children, Ilorin.

Mots clés: Bactériémie, Paludisme sévère, Enfants, Ilorin.

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Abbreviations: EPU, Emergency Paediatric Unit; GCS, Glasgow Coma Score; IQR, Inter Quartile Range; NTS, Non-Typhoidal *Salmonella*; RDT, Rapid Diagnostic Test; SPSS, Statistical Package For Social Sciences; UITH, University of Ilorin Teaching Hospital; WHO, World Health Organisation.

INTRODUCTION

Malaria remains a significant cause of morbidity and mortality globally with an estimated 228 million cases and 405,000 deaths in 2018.¹ Over 90% of the disease burden occurs in sub-Saharan Africa with Nigeria responsible for 25% of the global burden and 24% of deaths worldwide.¹ In Nigeria, there are 53 million cases of malaria with over 80,000 deaths, the majority of which occurs in children under 5.²

Malaria also remains a leading cause of hospital admissions in the tropics and the coexistence of the disease with bacteraemia has been documented among children.^{3,4} The presence of bacteraemia in children with severe *Plasmodium falciparum* malaria is associated with increased risk of morbidity and mortality.⁴⁻⁶ A systematic review found a case fatality of 24.1% among children with severe malaria and concomitant bacterial infections when compared to 10.2% in children with severe malaria alone in sub-Saharan Africa.⁵

The isolated organisms from other studies include non-typhoidal *Salmonella* (NTS) species,^{7,8} *Staphylococcus aureus*,^{9,10} *Streptococcus pneumoniae*^{4,11} and enteric gram-negative rods such as *Escherichia coli*,^{4,12} and *Pseudomonas aeruginosa*.^{4,9}

The increased risk of developing bacterial infections in children with severe malaria has brought to the fore the need for evidence to guide the management of the febrile child by clearly defining the burden and coexistence of both conditions using improved diagnostic tools and techniques.¹³ Majority of studies in Africa evaluating concomitant malaria and bacteraemia used conventional blood culture methods (Brain heart infusion,^{4,7} Glucose broth^{14,15}) to isolate organisms. However, newer automated continuous monitoring systems have improved ability to detect bacterial growth even when bacteria are present in small quantities.¹⁶ Furthermore, these automated blood culture systems can reduce antibiotic concentration in the culture broth and this would help improve the yield of organisms from the blood.¹⁷

Studies about severe malaria and concomitant bacteraemia in a high burden country like Nigeria have been relatively

few.^{11,18,19} The available surveys also lack uniformity in the selection of malaria subjects with the age group of the subjects ranging from infancy to adolescence. Furthermore, the report of blood stream infections in children with severe malaria have not been characterized by their association with the subsets of severe malaria.

This study therefore aimed to identify the magnitude and clinical significance of bacteraemia in children with severe malaria by identifying the subset of severe malaria at increased risk, the nature of isolated bacterial pathogens and the drug sensitivity pattern in this environment which will significantly guide empirical treatment. This is with the view that the findings will contribute towards reducing morbidity and mortality of severe malaria in Nigeria, sub-Saharan Africa and the world at large.

SUBJECTS, MATERIALS AND METHODS

Study Design and Location

This was a hospital-based descriptive cross-sectional study carried out at the Emergency Paediatric Unit (EPU) of the University of Ilorin Teaching Hospital (UITH), a tertiary healthcare facility in North Central Nigeria. The study was carried out from February – December 2018.

The UITH serves as a referral hospital for patients in the state and some surrounding states like Oyo, Osun, Kogi, Niger and Ekiti States from the North central and South western regions of the country. The EPU of UITH is a thirty-five bed ward manned by a lead consultant with other consultants coming in to take over the care of children admitted into their units within 24 hours of admission. There are also resident doctors, interns and nurses that always cover the EPU. The unit receives paediatric medical emergencies beyond the neonatal age up to the age of 14 years. About 1200 to 1900 children are admitted annually to the EPU with severe malaria accounting for about 15% of admissions.²⁰

The EPU has facilities for oxygen delivery, radiant heaters, and a functional side laboratory. All febrile children presenting in the EPU routinely have a

rapid diagnostic test for malaria done as part of a diagnostic workup.

Study Population

The study population consisted of children aged 6 months to 14 years presenting to the Emergency Paediatric Unit of the hospital with clinical and laboratory features of severe malaria.

Ethical Approval

Ethical clearance was obtained from the University of Ilorin Teaching Hospital Ethics Review Committee. Written informed consent was obtained from the care givers/parents. Additionally, informed assent was obtained in children aged seven years and older.

Sample Size Determination

The required sample size was calculated using the statistical formula for estimating minimum sample size in descriptive health studies for a population more than 10,000.²¹ The prevalence of severe malaria from the paediatric department records of the hospital was estimated to be 11.8%.²⁰ The calculated sample size was 160 and allowing for a non-response rate of 10%, the minimum sample size estimated was 176.

Sampling Technique

Children presenting into the Emergency Paediatric Unit (EPU) who fulfilled the inclusion criteria were consecutively recruited until the required sample size was attained. Eligible children had an initial rapid diagnostic test (RDT) for malaria. Those with positive RDT results had microscopic evaluation for estimation of parasitaemia. Children with microscopically confirmed parasitaemia in the presence of clinical and/or features of severe malaria were recruited into the study.

Case Definition of Severe Malaria²²

A severe malaria case was defined as a positive blood film for plasmodium specie with at least one of the following features listed below:

- Impaired consciousness - Blantyre Coma Score < 3 in children less than 5 years or Glasgow Coma Score < 11 in children greater than 5 years.
- Multiple convulsions: more than two episodes within 24 hours.

- Prostration – generalised body weakness so that the person is unable to sit, stand or walk without support.
- Acidosis-manifesting as respiratory distress (rapid, deep and laboured breathing).
- Circulatory collapse with systolic blood pressure less than 70 mmHg in children.
- Significant bleeding- this includes prolonged or recurrent nose or gum bleeds; bleeding from venepuncture sites; haematemesis or melaena.
- Clinical jaundice plus evidence of any vital organ dysfunction.
- Severe anaemia (Haemoglobin concentration $\leq 5\text{g/dL}$ or packed cell volume $\leq 15\%$ in children).
- Hypoglycaemia ($<2.2\text{mmol/L}$ or 40mg/dL).
- Hyperparasitaemia- *Plasmodium falciparum* parasitaemia $> 10\%$ or *Plasmodium knowlesi* $> 2\%$.
- Renal impairment (serum creatinine $> 265\mu\text{mol/L}$ or urea $> 20\text{mmol/L}$).

Inclusion Criteria

- All children presenting to the Emergency Paediatric Unit (UITH) aged between 6 months and 14 years with clinical and/or laboratory features of severe malaria.
- Children whose parents gave informed consent.

Exclusion Criteria

- Children with background neurologic disorder like cerebral palsy and seizure disorder were excluded from the study.
- Children whose blood films were negative for malaria parasite.

Data Collection

Clinical Features

The resident doctors are the first on call at the EPU and have been trained in the management of severe malaria with capacity to identify the presence of severe malaria defining conditions. They evaluated and made initial diagnosis, but a member of the research team (particularly AO) was present within an hour of admission to confirm diagnosis and record relevant clinical features in the study proforma. AA, OM and OA

were also available to further review the patient and affirm the diagnosis of severe malaria. The information obtained included the socio-demographic characteristics of the subjects' history of fever, convulsion, impaired neurological function, renal dysfunction, and abnormal bleeding. Physical examinations such as level of consciousness (using the Glasgow or Blantyre Coma Scores), hydration status, pallor, temperature, and basic anthropometry (after calibrating the tools) were all documented.

Laboratory Parameters

Every child had an initial needle prick for a capillary blood test for malaria, using a rapid malaria diagnostic test strip (SD Malaria Antigen P.f., Standard Diagnostics INC, USA, 2016). This was to allow the rapid institution of antimalarial treatment if the test was positive. Antibiotics was not instituted at this point. Those with positive rapid malaria diagnostic test then had a blood film for malaria parasite for microscopic evaluation. The blood films for *Plasmodium falciparum* were made and reviewed by a World Health Organization (WHO) certified microscopist. Thick films were examined for both parasite identification and density while thin films were evaluated for speciation.

Blood samples were collected in a well-illuminated room under strict aseptic measures into appropriately labelled Ethylene Diamine Tetraacetic Acid (EDTA), Lithium heparin and blood culture bottles (BACTEC™ PEDS PLUS/F vial).

A peripheral vein was located and the area around the vein was swabbed using a soaked cotton wool ball containing 70% alcohol. Thereafter, povidone iodine was applied followed by another alcohol swab. A tourniquet was applied about 6–8 cm above the identified vein and six millilitres of blood was withdrawn. A drop of blood was used for a random blood sugar using ACCU CHECK compact plus glucometer.

The flip-off cap of the blood culture bottle was removed, and the top cleaned with a 70% alcohol swab and allowed to dry. The needle used for blood sample collection was disposed in a sharps box and a new needle was then attached to

the syringe to inoculate the culture medium with 3 millilitres of blood, 2 millilitres into an EDTA bottle for a complete blood count as well as thick and thin film for malaria parasite and 1 millilitre of blood into a Lithium heparin bottle for serum Urea and Creatinine estimation. A heparinised capillary tube was used to take blood from the EDTA bottle for a side lab packed cell volume estimation (using haematocrit centrifuge).

The properly labelled blood culture bottles were sent to the laboratory within an hour of collection, processed and analyzed by a medical microbiologist. The blood culture samples were analysed using BACTEC™ 9120, a continuous culture monitoring system (Becton Dickinson, Temse, Belgium) which is an automated microbiology growth and detection system made to detect microbial growth from blood specimens. Following evidence of viable microbial growth, the rubber bung of the blood culture bottle was disinfected with 70% alcohol, aliquots were obtained and subjected to gram stain microscopy and sub-cultured on standard media plates (Chocolate, Blood and MacConkey agar) and incubated aerobically at 37°C .²³ Standard biochemical tests were used for full identification of the organisms.²⁴ Coagulase test was carried out on all catalase positive Gram positive isolates to differentiate between *Staphylococcus aureus* from other Coagulase negative *Staphylococcus* species. Antimicrobial susceptibility was determined using the disc diffusion method (modified by Kirby-Bauer technique and standardised by Clinical and Laboratory Standards Institute-CLSI).²⁵ Every child, whose blood grew at least one pathogenic bacteria organism, was considered to be bacteraemic.²⁶ Vials with no signals after five days were still subjected to Gram staining and sub-cultured before being discarded as negative. The patients who had bacterial isolates received antibiotics after drug sensitivity results from their blood cultures were received.

Lumbar puncture to obtain cerebrospinal fluid for analysis (Biochemistry, Microscopy, Culture and Sensitivity) was carried out for children with convulsions, altered consciousness or coma to determine the presence or absence of meningitis.

Complete Blood Count was carried out using an automated haematology analyser (Sysmex XE haematology analyser, Kobe Japan) based on the principle of flow cytometry.

Statistical Analysis

All the data obtained were analysed using statistical package for social sciences (SPSS) version 20.0 for Windows (IBM Corp., New York, USA). The variables were presented in frequency tables and charts and cleaned for errors. Pearson's Chi-squared test was used to compare proportions of categorical variables as appropriate. The odds ratio was used for an association between bacteraemia and outcome. The confidence level was set at 95%. Relationships between normally distributed continuous variables and a depended outcome variable were tested using the Student's t-test once the assumptions are met, else a non-parametric test was applied. Logistic regression was used to examine clinical features of severe malaria which predicted bacteraemia. Statistical significance was defined as p-value <0.05.

RESULTS

Socio-demographic Characteristics

A total of 944 children aged 6 months–14 years with severe malaria were admitted in the Emergency Paediatric Unit (EPU) during the study period. The overall number was lower than previous years due to industrial actions that disrupted services. Of this number, 181 had positive rapid diagnostic tests for malaria and clinical/ laboratory features of severe malaria. However, 5 of the children with positive rapid diagnostic test for malaria were excluded because of absence of malaria parasite on microscopy. This is not an uncommon experience due to the extended period of sensitivity of HRP-2 based RDTs even after the parasites are no longer viable.²⁷ Therefore, 176 children who met the inclusion criteria for the study were recruited. Among the children recruited, 50.6% were aged between the ages of 6 months and 5 years. Male subjects were 108 (61.4%) with a male: female ratio of

1.6: 1. All recruited children had blood culture done.

Medical History of Recruited Subjects

All the subjects had a history of fever at presentation. There was a history of prostration in 74 (42.0%) and multiple convulsions in 59 (33.5%). There were 57 (32.4%) subjects with impaired consciousness. Other presenting symptoms in the subjects in decreasing frequency include passage of dark coloured urine in 42 (23.9%), difficulty in breathing in 23 (13.1%), history of reduction in urine volume in 4 (2.3%) and abnormal bleeding in 4 (2.3%).

Proportion of Children with Severe Malaria and Concomitant Bacteraemia.

Regarding concomitant bacterial infection, 41 of the 176 subjects (23.3%) had positive blood culture of pathogenic bacteria. Of the 41 subjects with concomitant bacteraemia, 23 (56.1%) were male. Children aged 6 months –< 5 years with concomitant bacteraemia were 23 (25.8%). There was no significant difference in gender and age distribution between children with severe malaria with concomitant bacteraemia and those without bacteraemia. (p = 0.429 and 0.403 respectively) as shown in Table 1.

Table 2 illustrates the distribution of subjects based on the clinical diagnosis of severe malaria as well as the presence of bacteraemia. The major forms of severe malaria with clinical diagnosis at admission were severe anaemia (39; 22.2%), prostration (39; 22.2%), multiple convulsion (26; 14.8%) and cerebral malaria (26; 14.8%). Of the 41 children with

concomitant bacteraemia, 8 (19.5%) had severe anaemia while 7 (17.1%) each had prostration and multiple convulsions respectively, 6 (14.6%) of them had cerebral malaria and others as shown in Table 2.

The relationship between the presence of bacteraemia and the number of clinical diagnosis is shown in Table 3 below. The relationship between the number of clinical diagnosis and concomitant bacteraemia was not statistically significant (p = 0.576).

Bacterial Agents (Organisms) Isolated from Blood of Children admitted with Severe Malaria

Overall, gram positive pathogens were isolated in 29 (70.7%) subjects with bacteraemia while gram negative pathogens were isolated in 12 subjects (29.3%).

Staphylococcus aureus isolates, 27 (65.9%) was the predominant bacterial isolate followed by *Pseudomonas aeruginosa* 4 (9.8%), *Klebsiella pneumoniae* 3 (7.3%), and non-typhoidal *Salmonella* 2 (4.9%), *Enterococcus faecalis* 2 (4.9%), and 1 (2.4%) each of *Escherichia coli*, *Salmonella typhi* and *Acinetobacter baumannii* as shown in Table 4.

Drug Sensitivity Pattern

Staphylococcus aureus isolates were most sensitive to Gentamycin (23; 92.0%) and followed by Amoxicillin/Clavulanic acid (22; 88.0%). The two Methicillin Resistant *Staphylococcus Aureus* (MRSA) isolates were sensitive to Vancomycin.

Table 1: Relationship between Gender, Age Group and the Occurrence of Concomitant Bacteraemia among Subjects with Severe Malaria

	Bacteraemia		χ^2	p value
	Yes n = 41(%)	No n = 135(%)		
Gender				
Male	23 (56.1)	85 (63.0)	0.625	0.429
Female	18 (43.9)	50 (37.0)		
Age (years)				
6 months –< 5	23 (25.8)	66 (74.2)	1.819	0.403
5 – < 10	16 (23.2)	53 (76.8)		
10 – 14	2 (11.1)	16 (88.9)		
Median (IQR)	36.0 (30.0–72.0)	60.0 (36.0–72.0)		

Table 2: Distribution of Subjects based on Clinical Diagnosis of Severe Malaria and the Presence of Bacteraemia

Clinical diagnosis	Frequency (%)	Bacteraemia (%)
Severe anaemia	39 (22.2)	8 (19.5)
Prostration	39 (22.2)	7 (17.1)
Multiple convulsion	26 (14.8)	7 (17.1)
Cerebral malaria	26 (14.8)	6 (14.6)
Cerebral malaria + Severe anaemia	17 (9.7)	3 (7.3)
Severe anaemia + Jaundice	5 (2.8)	2 (4.9)
Cerebral malaria + Severe anaemia + Jaundice	4 (2.3)	1 (2.4)
Cerebral malaria + Jaundice	2 (1.1)	0 (0.0)
Severe anaemia + Multiple convulsion	2 (1.1)	2 (4.9)
Prostration+ Hyperparasitaemia	2 (1.1)	1 (2.4)
Severe anaemia + Hypoglycaemia	2 (1.1)	0 (0.0)
Cerebral malaria + Severe anaemia + Significant bleeding	2 (1.1)	1 (2.4)
Cerebral malaria + Severe anaemia + Jaundice + Renal impairment	2 (1.1)	1 (2.4)
Cerebral malaria + Renal impairment + Circulatory collapse	1 (0.6)	1 (2.4)
Cerebral malaria + Severe anaemia + Renal impairment	1 (0.6)	0 (0.0)
Cerebral malaria + Severe anaemia + Renal impairment + Significant bleeding	1 (0.6)	0 (0.0)
Cerebral malaria + Severe anaemia + Jaundice+ Circulatory collapse + Significant bleeding	1 (0.6)	1 (2.4)
Multiple convulsion + Hyperparasitaemia	1 (0.6)	0 (0.0)
Severe anaemia + Renal Impairment	1 (0.6)	0 (0.0)
Severe anaemia+ Hypoglycaemia+ Jaundice	1 (0.6)	0 (0.0)
Severe anaemia + Hyperparasitaemia	1 (0.6)	0 (0.0)
Total	176 (100.0)	41 (100.0)

Table 3: Bacteraemia according to the Number of Clinical Diagnosis

Number of Components	Number of Subjects	Bacteraemia (%)	Absence of Bacteraemia (%)	χ^2	p value
One	130	28 (21.5)	102 (78.5)	1.102 ^y	0.576
Two	33	8 (24.2)	25 (75.8)		
Three	9	3 (33.0)	6 (66.7)		
Four	3	1 (33.0)	2 (66.7)		
Five	1	1 (100.0)	0 (0.0)		

Table 4: Spectrum of Pathogenic Bacterial Isolates from Blood Cultures of Subjects

Pathogenic Organisms	Frequency n= 41 (%)
Gram Positive bacteria	29 (70.7)
<i>Staphylococcus aureus</i>	27 (65.9)
<i>Enterococcus faecalis</i>	2 (4.9)
Gram Negative bacteria	12 (29.3)
<i>Pseudomonas aeruginosa</i>	4 (9.8)
<i>Klebsiella pneumoniae</i>	3 (7.3)
Non-typhoidal <i>Salmonella</i>	2 (4.9)
<i>Escherichia coli</i>	1 (2.4)
<i>Salmonella typhi</i>	1 (2.4)
<i>Acinetobacter baumannii</i>	1 (2.4)

All 4 (100.0%) *Pseudomonas aeruginosa* isolates were sensitive to Ciprofloxacin, Ceftazidime and Imipenem and all 4 (100.0%) were resistant to Amoxicillin/Clavulanic acid, Azithromycin, Ceftriaxone, Cefuroxime and Gentamycin. Three (75.0%) isolates of *Pseudomonas aeruginosa* were sensitive to Piperacillin-Tazobactam. The drug sensitivity patterns of other isolates are as shown in Table 5 and Table 6.

Predictors of Bacteraemia in Children with Severe Malaria

Table 7 shows the binary regression analysis of the clinical parameters that predicted the presence of bacteraemia in the recruited subjects. The parameters which were significantly associated with bacteraemia on the initial univariate analysis (tachycardia, splenomegaly, duration of coma before presentation and temperature) were included in the binary regression analysis.

Duration of coma before presentation was found to be the only significant predictor of bacteraemia in children with severe malaria with an odd ratio of 1.7 (95% CI 1.1–2.6) for every additional day of coma.

The Effect of Concomitant Bacteraemia on Treatment Outcome

The median (IQR) duration of admission in subjects with concomitant bacteraemia [4.0 (3.0–5.0)] was significantly higher than in those without concomitant bacteraemia [3.0 (3.0–5.0); $p=0.028$]. Likewise, the median (IQR) fever clearance time in subjects with concomitant bacteraemia [2.0 (1.3–3.0)] was significantly higher than in those without concomitant bacteraemia [1.5 (1.0–2.0); $p=0.015$]. Thirteen of the 176 subjects died, giving a percentage mortality of 7.4%. Five (38.5%) out of the 13 children who died had severe malaria and concomitant bacteraemia. The case fatality rate (CFR) of severe malaria alone was 5.9% (8 of the 135 subjects), however, increased to 12.2% in children with concomitant bacteraemia (5 of the 41 subjects). This difference was however not statistically significant ($p=0.185$). The median age (IQR) in subjects who died was 60.0 (36.0–79.0) months while the median age (IQR) in subjects who were discharged was 54.0 (30.0–72.0) months.

Table 5: Drug Sensitivity Pattern of Bacterial Isolates (Gram-Positive Pathogens)

Isolate		AMC	AZM	CRO	CXM	CIP	GM	VA	CAZ	IMI	PTZ
<i>Staphylococcus aureus</i> (n = 25)	S	22(88.0)	12(48.0)	18(72.0)	16(64.0)	21(84.0)	23(92.0)	NT	NT	NT	NT
	R	3(12.0)	13(52.0)	7(28.0)	9(36.0)	4(16.0)	2(8.0)	NT	NT	NT	NT
Methicillin Resistant <i>Staphylococcus aureus</i> (n = 2)	S	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(100.0)	NT	NT	NT
	R	2(100.0)	2(100.0)	2(100.0)	2(100.0)	2(100.0)	2(100.0)	0(0.0)	NT	NT	NT
<i>Enterococcus faecalis</i> (n = 2)	S	1(50.0)	1(50.0)	2(100.0)	2(100.0)	2(100.0)	0(0.0)	NT	NT	NT	NT
	R	1(50.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)	2(100.0)	NT	NT	NT	NT

***AMC**, Amoxicillin-Clavulanic Acid; **AZM**, Azithromycin; **CRO**, Ceftriaxone; **CXM**, Cefuroxime; **GM**, Gentamycin; **VA**, Vancomycin; **CAZ**, Cefazidime; **IMI**, Imipenem; **PTZ**, Piperacillin-Tazobactam; **S**, Sensitive; **R**, Resistant; **NT**, Not tested.

Table 6: Drug Sensitivity Pattern of Bacterial Isolates (Gram-Negative Pathogens)

Isolate		AMC	AZM	CRO	CXM	CIP	GM	VA	CAZ	IMI	PTZ
<i>Pseudomonas aeruginosa</i> (n = 4)	S	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(100.0)	0(0.0)	NT	4(100.0)	4(100.0)	3(75.0)
	R	4(100.0)	4(100.0)	4(100.0)	4(100.0)	0(0.0)	4(100.0)	NT	0(0.0)	0(0.0)	1(25.0)
<i>Klebsiella pneumoniae</i> (n = 2)	S	1(50.0)	0(0.0)	1(50.0)	0(0.0)	1(50.0)	2(100.0)	NT	1(50.0)	2(100.0)	2(100.0)
	R	1(50.0)	2(100.0)	1(50.0)	2(100.0)	1(50.0)	0(0.0)	NT	1(50.0)	0(0.0)	0(0.0)
Non-typhoidal <i>salmonella</i> (n = 2)	S	1(50.0)	0(0.0)	2(100.0)	1(50.0)	2(100.0)	2(100.0)	NT	2(100.0)	2(100.0)	2(100.0)
	R	1(50.0)	2(100.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)	NT	0(0.0)	0(0.0)	0(0.0)
<i>Escherichia coli</i> (n = 1)	S	1(100.0)	0(0.0)	1(100.0)	1(100.0)	1(100.0)	1(100.0)	NT	0(0.0)	1(100.0)	0(0.0)
	R	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	NT	1(100.0)	0(0.0)	1(100.0)
<i>Salmonella typhi</i> (n = 1)	S	1(100.0)	0(0.0)	1(100.0)	1(100.0)	1(100.0)	1(100.0)	NT	1(100.0)	0(0.0)	0(0.0)
	R	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	NT	0(0.0)	1(100.0)	1(100.0)
<i>Acinetobacter baumannii</i> (n = 1)	S	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(100.0)	1(100.0)	NT	1(100.0)	1(100.0)	1(100.0)
	R	1(100.0)	1(100.0)	1(100.0)	1(100.0)	0(0.0)	0(0.0)	NT	0(0.0)	0(0.0)	0(0.0)

***AMC**, Amoxicillin-Clavulanic Acid; **AZM**, Azithromycin; **CRO**, Ceftriaxone; **CXM**, Cefuroxime; **GM**, Gentamycin; **VA**, Vancomycin; **CAZ**, Cefazidime; **IMI**, Imipenem; **PTZ**, Piperacillin-Tazobactam; **S**, Sensitive; **R**, Resistant; **NT**, Not tested.

Table 7: Binary Regression Analysis of Characteristics that Predict Bacteraemia in Children with Severe Malaria

Variable	OR	95% CI	p value
Tachycardia	0.5	0.1 – 2.4	0.383
Splenomegaly	0.0	0.0	0.999
Increasing duration of coma before presentation (days)	1.7	1.1 – 2.6	0.010
Body Temperature (°C)	1.2	0.6 – 2.2	0.651

OR, Odds ratio; CI, Confidence interval; Nagelkerke $R^2 = 45.3\%$.

DISCUSSION

The prevalence of bacteraemia in children with severe malaria in this study was 23.3% which is a relatively high figure when compared to previous reports from various countries in sub-

Saharan Africa which varied from 4.6% to 20.8%.^{7,18,19,28–30} The higher prevalence recorded in this study may have been due to the inclusion all severe malaria components as well as the utilization of automated blood culture system which

contains resins that effectively reduce the antibiotic concentration in culture broth and increase microbial yield.¹⁷ There are a number of factors that have been suggested as influencing the occurrence of bacteria co-infection in severe malaria. These include suppressed circulating bicyclo-PGE2 levels and leukocyte COX-2 transcripts in children co-infected with *P. falciparum* malaria and HIV-1 or bacteraemia,³¹ L-arginine deficiency, which is associated with intestinal mastocytosis, elevated levels of histamine, and enhanced intestinal permeability increasing susceptibility to infection,³² and increases levels of mediators of inflammation such as interleukin.³³ This study was unable to explore these factors, but it is likely that the levels of some of these substances could have been affected by the level of malaria endemicity and increased susceptibility to bacteria co-infection. Additionally, the study by Bronzan *et al*⁷ did not include all severe malaria components and was limited to children with cerebral malaria and severe anaemia. Likewise, Enwere *et al*¹⁰ and Prada *et al*¹⁸ included only subjects with cerebral malaria, meaning that some cases of bacteraemia may have been undetected. The studies by Berkley *et al*,⁴ Bronzan *et al*,⁷ and Evans *et al*⁸ used brain heart infusion as the culture medium while Enwere *et al*¹⁰ used tryptone soy broth and thioglycolate broth.

A comparison of age and bacterial co-infection showed that there was a statistically similar preponderance of bacterial infection in children aged 6 months to 5 years when compared to children older than 5 years. Evans *et al*⁸ who also had subjects with a wide age range (4 months–11 years) reported a higher prevalence of bacteraemia in younger children. Similarly, Berkley *et al*⁴ and Bronzan *et al*⁷ both reported that bacteraemia was more common in younger children though the exact age range of their study population was not reported. This finding may be due to the fact that younger children have increased susceptibility to infections because of their underdeveloped immune system.³⁴ It has been reported that children who are less than 3 years old with severe malaria have impaired immunological

response of the spleen, thus predisposing them to bacterial infections.³⁴ This brings to fore the need to aggressively look out for concomitant bacteraemia in younger subjects with severe malaria.

Gram positive organisms were predominant in this study and this is similar to observations by Berkley *et al*⁴, Ayoola *et al*¹⁴ and Angyo *et al*.¹¹ *Staphylococcus aureus* was the most predominant pathogen isolated corroborating findings by Akpede *et al*³⁵ in Benin, Nigeria and Enwere *et al*¹⁰ in Banjul, the Gambia; accounting for 39.5% and 42.9% of isolates respectively. *Staphylococcus aureus* is also a common cause of childhood bacterial infections from previous studies across Nigeria³⁶⁻³⁹ and the high prevalence of *Staphylococcus aureus* infections may be due to its importance as a cause of both community acquired and hospital acquired infections. The yield could also have been high because of the increasing widespread vaccinations which could reduce the incidence of *Haemophilus influenza* and *Streptococcus pneumoniae*. In previous studies in sub-Saharan Africa, NTS was identified to be the predominant bacterial isolate in children with severe malaria.^{7,8} However, NTS did not contribute significantly to the pathogens isolated in this study which is in tandem with previous studies in the country. This shows that NTS may have a lesser role as a cause of bacteraemia in Nigeria.

The gram positive organisms isolated in the subjects were mostly sensitive to Amoxicillin-Clavulanic Acid, Ciprofloxacin, and Gentamycin while the gram negative organisms were mostly sensitive to Ciprofloxacin and Imipenem. Another important observation in this study is the varied distribution of organisms and their antibiotic susceptibility pattern when compared with other studies. From the antibiogram in this study, a rational choice of antibiotic in children with severe malaria and clinical suspicion of bacteraemia is Ciprofloxacin which has a good gram-positive and gram-negative coverage.

The single most important predictor of bacteraemia in severe malaria found in this study was increasing duration of

coma before presentation. This indicates that clinicians should have a high index of suspicion for concomitant bacteraemia in children with severe malaria who are comatose. Children with concomitant bacteraemia were also identified to have a higher case fatality rate than children with severe malaria alone which is similar with observations by Bronzan *et al*⁷ and Bassat *et al*.²⁹ These findings further reinforce the fact that concomitant bacteraemia worsens clinical course of severe malaria. The duration of admission and fever clearance time were also significantly prolonged in children with concomitant bacteraemia. Though there is paucity of information from previous reports as regards the effect of concomitant bacteraemia on this outcome parameters, these findings may serve as a template for future research.

Our study was not without limitations as the small number of children with other forms of severe malaria (asides severe anaemia, prostration, cerebral malaria, and multiple convulsion) limited the power of the study to relate them with bacteraemia. In addition, the number of blood cultures done was limited to the one taken at admission. A serial blood culture may have improved the yield of organisms. However, this study provides very germane information regarding this very important aspect of malaria care and provides a framework for future multicentre studies in line with reducing the scourge associated with the disease.

CONCLUSION

The prevalence of bacteraemia in the children with severe malaria was 23.3% with a greater proportion being among under 5 children. Gram positive pathogens constituted the predominant organisms with *Staphylococcus aureus* being the most common isolate (65.9%). The bacterial isolates (both gram positive and negative) were mostly sensitive to Ciprofloxacin. Increasing duration of coma prior to admission was the only independent predictor of the presence of bacteraemia in children with severe malaria.

There is therefore a need for children with severe malaria (particularly under-five children) to be evaluated for concomitant bacteraemia especially

those presenting with coma. Ciprofloxacin should also be considered as an empirical antibiotic of choice in children with severe malaria with concomitant bacteraemia in our environment.

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Competing Interests

The authors declare that they have no competing interests.

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