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Research Article

A Prospective Cohort Study of the Clinical Predictors of Bacteraemia in Under-Fives Children with Acute Undifferentiated Fever Attending a Secondary Health Facility in North-Western Nigeria

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ABSTRACT

Background: Children with acute febrile illness with no localizing signs often receive antibiotics empirically in most resource-poor settings. Little is however known about the burden of bacteraemia in this category of patients and an appraisal is thus warranted. This will guide clinical practice and promote rational antibiotics use.

Methods: We prospectively followed up 140 under-five children who presented with acute undifferentiated fever at the emergency/out-patient paediatric unit of a secondary healthcare facility. Baseline clinical and laboratory information were obtained and documented in a structured questionnaire. We compared baseline characteristics between participants with bacteraemia and those without bacteraemia. We further fitted a multivariable logistic regression model to identify factors predictive of bacteraemia among the cohort.

Result: The prevalence of bacteraemia was 17.1% and Salmonella typhi was the most frequently (40.9%) isolated pathogen. The majority (78.6%) of the study participants were managed as out-patients. The participants who required admission were thrice likely to have bacteraemia when compared to those managed as out-patients (AOR -3.66 95% CI -1.11 to 12.08). There is a 14% increase in the odds for Bacteraemia (AOR 1.14, 95% CI -1.02 to 1.27) with a daily increase in the duration of fever. Similarly, participants who were admitted with lethargy were 6.5 times more likely to have bacteraemia (AOR - 6.46, 95% CI -1.27 to 32.80). Other significant predictors were tachypnoea and lymphopenia.

Conclusion: Among under-five children with acute undifferentiated fever. Longer duration of fever, lethargy, in-patient care, tachypnea and lymphopenia were the significant predictors of bacteraemia.

Keywords: Acute Undifferentiated Fever; Bacteraemia; Lethargy; Lymphopenia; Salmonella; Under-five children

INTRODUCTION

An acute undifferentiated febrile illness is characterized by a fever of fewer than two weeks for which no localizing signs or aetiology is found after a full history and physical examination. [1,2] It may be the only symptom of a mild self-limiting illness or antecedent of a serious infection caused by a bacteria pathogen. [3, 4] Most cases of acute undifferentiated fever (AUF) are caused by viruses in South and South-east Asia while malaria parasitaemia has frequently been identified in parts of sub-Saharan Africa. [5-7]

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In most resource-poor settings, polymicrobial infection with viruses, bacteria and malaria is common and could be clinically indistinguishable.[8,10] Although, malaria could be rapidly diagnosed in most of these settings, clinicians in these settings are often challenged by the limited access to bacterial culture facilities to aid accurate diagnosis of bacteraemia.[11] Also, white blood cell parameters which are available are inadequate to differentiate between malaria, viral and bacterial pathogens. Hence, children with acute fever are often presumptively prescribed antibiotics and this could increase the risk of antibiotic resistance. [12, 13]

There is currently a dearth of information on the accurate burden of bacteraemia among children with AUF in most resource-poor settings especially in sub-Saharan Africa and this could jeopardize the rational deployment of antibiotics. Such epidemiological studies will be crucial, not only in identifying the bacterial aetiology of AUF but also in providing clinical predictors that could guide presumptive diagnosis. This study was initiated on a platform of ongoing surveillance for bacteraemia in young children to identify clinical predictors of bacteraemia among under-five children with acute undifferentiated fever.

MATERIALS AND METHODS

Study design and setting

A prospective cohort study conducted at the emergency and paediatric out-patient unit of Murtala Mohammed Specialist Hospital (MMSH), Kano. The Paediatric Department of the hospital has an out-patient unit, a 30-bedded emergency unit and a 50-bedded paediatric medical ward. On average, the department conducts about 200-300 paediatric emergency consultations daily and about 300 out-patient consultations daily. The emergency unit is manned by interns, medical officers and a consultant and receives paediatric medical emergencies beyond the neonatal age up to the age of 14 years while the out-patient unit is manned by medical officers and a supervising consultant.

Inclusion and exclusion criteria

Subjects were previously healthy under-five children aged from one month to 59 months with acute undifferentiated fever. Subjects known to have sickle cell disease (SCD) or those that have taken antibiotics/antimalarial 48 hours prior to recruitment were excluded. Children with SCD are mostly of routine antibiotics prophylaxis in the study location.

Sample size determination

The sample size of the study was 140 study participants. This was determined using the standard formula for sample size in an observational study. [14] The calculation for this is shown below:

$$n = \frac{z^2pq}{d^2}$$

Where n = the desired minimum sample size, z = the standard normal deviation set at 1.96 which corresponds to 95% confidence interval and p = the prevalence of bacteraemia among children with undifferentiated fever, estimated to be 9% from a previous study. [6] Also, q = 1 – p = 1 – 0.09 = 0.91 while d = tolerable margin of error, an observed difference of 5% is taken as being significant.

$$\text{Therefore, } n = \frac{1.96^2 \times 0.09 \times 0.91}{0.05^2} = 126$$

The calculated sample size was 126 and allowing for an attrition rate of 10% (≈13) the minimum sample size estimated was approximately 140.

Definitions

Acute undifferentiated fever: fever ≥38°C of ≤ 14 days without localized or organ-specific clinical features. Non-localizing symptoms include; myalgia, clear rhinorrhoea, non-bloody diarrhoea, rash, arthralgia, headache, altered sensorium, and jaundice.[6,15,16]

Bacteraemia: isolation of at least one non-contaminant bacteria from the admission blood specimen. Coagulase-negative Staphylococcus species, Corynebacterium species, α- or γ-hemolytic Streptococci, Micrococcus species, Bacillus species and Propionibacterium species were regarded as contaminants. [17]

Data Collection

Subjects fulfilling the pre-set clinical criteria were recruited consecutively during their presentation to the emergency or out-patient unit until the estimated sample size was achieved. This spans a period of five month (November 2015 and March 2016). The recruitment was done by a medical officer with at least two years of experience of pediatric emergency setting. Clinical history was obtained from the care-givers and same, alongside examination findings were entered in a study proforma. Each study participant was followed up until outcome. This was; Discharge, Death, Discharge against medical advice, Symptom free (outpatient) at 7 days follow-up or Unknown (outpatients that could not be reached by phone and who did not return for follow-up).

Complete blood count and bacterial isolation were automated using Swelab and BACTECTM 9050 respectively. All samples were sent to the laboratory within an hour of collection for incubation and the vials were incubated in the automated culture system for a maximum of five days. A positive reading indicates the presumptive presence of viable microorganisms in the vial usually within 48 hours. Under aseptic conditions, aliquots were obtained from positive vials. Aliquots were subjected to Gram stain microscopy and sub-cultured on standard media plates. [18] Thereafter, the full identification of the organisms was obtained by standard biochemical tests. [19]

All ill looking subjects as assessed by the attending clinician were hospitalized while subjects that were not ill-looking were

managed as outpatients. Lumbar puncture was performed on subjects with a recent history of convulsion or symptoms suggestive of meningeal irritation. Follow-up of all non-hospitalized subjects was performed by telephone contact and the parents were asked to return with the subjects for further assessment within 48 hours.

Exposure variables

We elicited most of our exposure variables by direct questioning. We derived some other variables, for example, high-grade fever was defined as a temperature greater than 40oC.[20] We also classified participants as having tachypnea based on their respiratory rate using the World health organization definitions :> 60 breaths per minute for children aged below 2 months, > 50 breaths per minute for children aged 2–11 months and > 40 breaths per minute for children aged 12–59 months. [21] Tachycardia was also defined based on the standard values for age, >160 beats per minute for infants < 1 year, >150 beats per minute for those between 1 and 2 years and >140 beats per min for ages between 2 and 5 years.[22] Other laboratory variables were also defined using standard values. Severe anaemia was defined as a packed cell value of less than 18% and thrombocytopenia as a platelet count below 150,000 cells/mm3. [23] Lymphopenia was defined as lymphocyte counts below 3 x 109/L, neutropenia as Neutrophils counts below 1 x 109/L and leucocytosis as white cell count >15 x 109/ L.[24]

Outcome variable

This was defined as the occurrence of bacteraemia

Data analysis

We provided participant summary statistics using the median and interquartile range for non-normally distributed data and frequencies with percentages for categorical data. We compared proportions using chi-square and when an expected cell count was less than 5 the Fischer's exact test was used. We also compared medians using the Man-Whitney U test. Statistical significance was set at p <0.05 for our univariable analysis. Significant predictors on univariable analyses were placed in a maximal logistic regression model containing all previously significant predictors. The least significant predictor (with a P-value of >0.05) was dropped using backwards stepwise regression until the final model which had only significant predictors. The co-efficient of the final model were exponentiated to derive adjusted odds ratios and their corresponding 95% confidence intervals. All statistical analyses were performed using STATA version 16.1 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP).

RESULTS

Between November 2015 and March 2016, 140 under-five children who presented with acute undifferentiated fever were recruited into this study. Of this number, we identified 24 (17.1%) with a positive blood culture and identified an organism in 22 (15.7%) of them. Salmonella Typhi was the most frequently cultured organism (40.9% of isolates; Figure 1) and this was followed by Non-typhi Salmonella (31.8% of isolates; Figure 1). Co-trimoxazole had the highest resistance among antibiotics as 77.8% and 85.7% of Salmonella Typhi and Non-typhi Salmonella were resistant to the antibiotic (Figure 1)

Figure1: Antibiogram showing relative frequencies of organisms grown on culture and their different sensitivity profiles.

Organism type	Frequency (%)	Sensitivity	Co-trim (%)	Aug (%)	Cefo (%)	Genta (%)	Cipro (%)	Ceftri (%)
Salmonella Typhi	9 (40.9)	Resistant	7 (77.8)	1 (11.1)	2 (22.2)	0 (0.0)	1 (11.1)	1 (11.1)
		Sensitive	2 (22.2)	7 (77.8)	6 (66.7)	9 (100.0)	8 (88.9)	8 (88.9)
		Not tested	0 (0.0)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
Non-typhi Salmonella	7 (31.8)	Resistant	6 (85.7)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Sensitive	1 (14.2)	4 (57.1)	6 (66.7)	7 (100.0)	7 (100.0)	7 (100.0)
		Not tested	0 (0.0)	1 (14.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
Streptococcus Pneumoniae	2 (9.0)	Resistant	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
		Sensitive	1 (50.0)	2 (100.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)
		Not tested	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	1 (50.0)
Salmonella Specie	1 (4.6)	Resistant	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
		Sensitive	1 (100.0)	0 (0.0)	1 (100.0)	1 (100.0)	0(0.0)	1 (100.0)
		Not tested	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Klebsiella specie	1 (4.6)	Resistant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Sensitive	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
		Not tested	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Proteus Mirabilis	1 (4.6)	Resistant	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Sensitive	0 (0.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
		Not tested	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stenotrophomonas Maltophilia	1 (4.6)	Resistant	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Sensitive	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	1 (100.0)	1 (100.0)
		Not tested	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	22 (100.0)	Resistant	15 (68.2)	4 (18.2)	2 (9.1)	1 (4.6)	2 (9.1)	1 (4.5)
		Sensitive	7 (31.8)	16 (72.3)	16 (72.3)	21 (95.5)	19 (86.4)	20 (91.0)
		Not tested	0 (0.0)	2 (9.1)	4 (18.2)	0 (0.0)	1 (4.5)	1 (4.5)

Yellow - Gram-Negative organism. Blue - Gram-positive organism Red – Resistance of organism >70% of species, Brown - Resistance of organism between 50 and 70% of species.

Abbreviations Cotrim – Co-trimoxazole, Aug – Amoxicillin-clavulanate, Cefo- Cefotaxime, Genta – Gentamicin, Cipro – Ciprofloxacin and Ceftri – Ceftriaxone.

Participant outcomes

Thirty enrollees (22.4%) were hospitalized while 110 (78.6%) were managed as out-patients. Ninety-two (83.7%) out-patients were identified symptom-free after a 7-day follow-up, while 18 (16.4%) were lost to follow-up. Among the in-patients, 22 (73.3%) were discharged, 3 (10.0%) discharged against medical advice and 5 (16.7%) died while on admission

Participant sociodemographic and clinical characteristics

The median duration of fever was significantly higher in the bacteraemia group (6.5 days) when compared to the group without bacteraemia (4 days, p=0.008, Table 1). Similarly, bacteraemia occurred more frequently among children admitted as inpatients (p=0.001, Table 1) and presented clinically with a history of lethargy (0.02, Table 1). There was no significant difference in gender, age distribution or clinical histories of rhinorrhoea, poor feeding, diarrhoea, vomiting, convulsions, fast breathing, abdominal pain and abdominal distension between the two groups.

Table1: Participant sociodemographic characteristics and clinical history compared between those with bacteraemia and those without.

Variable	Bacteraemia (%) n=24	No Bacteraemia (%) n=116	P-value	Total (%) n= 140
Age (months)				
≤12	3 (12.5)	17 (14.7)	0.80	20 (14.3)
13 to 24	6 (25.0)	35 (30.2)		41 (29.3)
25 to 59	15 (62.5)	15 (62.5)		79 (56.4)
Gender				
Male	14 (58.3)	63 (54.3)	0.72	77 (55.0)
Female	10 (41.7)	53 (45.7)		63 (45.0)
Median duration of fever* (IQR)	6.5(7.5) days	4 (5.0) days	0.008	4 (4.0)
Hospitalization				
No	13 (54.2)	97 (83.6)	0.001	110 (78.6)
Yes	11 (45.8)	19 (16.4)		30 (21.4)
Rhinorrhoea				
Yes	11 (45.8)	56 (48.3)	0.83	67 (47.9)
No	13 (54.2)	60 (51.7)		73 (52.1)
Poor feeding&				
Yes	4 (16.7)	40 (34.5)	0.10	44 (31.4)
No	20 (83.3)	76 (65.5)		96 (68.6)
Diarrhoea				
Yes	13 (54.2)	40 (34.5)	0.07	53 (37.9)
No	11 (45.8)	76 (65.5)		87 (62.1)
Vomiting				
Yes	9 (37.5)	35 (30.2)	0.48	44 (31.4)
No	15 (62.5)	81 (69.8)		96 (68.6)
Convulsions &				

Yes	2 (8.3)	11 (9.5)	1.00	13 (9.3)
No	22 (91.7)	105 (90.5)		127 (90.7)
Fast breathing&				
Yes	2 (8.3)	8 (6.9)	0.68	10 (7.1)
No	22 (91.7)	108 (93.1)		130 (92.9)
Abdominal pain				
Yes	5 (20.8)	10 (8.6)	0.08	15 (10.7)
No	19 (79.1)	106 (91.4)		125 (89.3)
Abdominal distension &				
Yes	1 (4.2)	3 (2.6)	0.53	4 (2.9)
No	23 (95.8)	113 (97.4)		136 (97.1)
Lethargy				
Yes	7 (6.0)	5 (20.8)	0.02	12 (8.6)
No	109 (94.0)	19 (79.2)		128 (91.4)
Tachycardia				
Absent	11 (45.8)	83 (71.6)	0.02	94 (67.1)
Present	13 (54.2)	33 (28.5)		46 (32.9)
Tachypnea				
Absent	11 (45.8)	84 (72.4)	0.01	95 (67.9)
Present	13 (54.2)	32 (27.6)		45 (32.1)
Thrombocytopenia*				
Absent	15 (75.0)	76 (83.5)	0.37	91 (82.0)
Present	5 (25.0)	15 (16.5)		20 (18.0)
Severe anaemia*				
Absent	21 (95.5)	90 (93.8)	0.76	111 (94.1)
Present	1 (4.6)	6 (6.3)		7 (5.9)
Lymphopenia*				
Absent	10 (45.5)	67 (69.1)	0.036	77 (64.7)
Present	12 (54.6)	30 (30.9)		42 (35.3)
Neutropaenia*				
Absent	20 (90.9)	87 (89.7)	0.86	107 (89.9)
Present	2 (9.1)	10 (10.3)		12 (10.1)
White cell count*				
Normal	18 (81.8)	64 (66.0)	0.018	82 (68.9)
Leucocytosis	0 (0.0)	25 (25.8)		25 (21.0)
Leucopenia	4 (18.2)	8 (8.3)		-10.1

& - Fischer's exact test performed.

*- Missing data, not all participants had blood samples taken

Participant clinical examination and laboratory findings

A significantly higher proportion of participants in the bacteraemia group (25.0%) presented with a high-grade fever when compared to those without bacteraemia (75.0%, p=0.013, Table 2). Similarly, a significantly greater proportion of the bacteraemia group presented with tachycardia (p=0.02), tachypnoea (0.01) and lymphopenia (0.036). The distribution of white cell count also differed across both groups (p=0.018, Table 2). There were no significant group differences in thrombocytopenia, severe anaemia and neutropenia.

Table2: Participant clinical examination and laboratory findings compared between those with bacteraemia and those without.

Variable	Bacteraemia (%) n=24	No Bacteraemia (%) n=116	P-value	Total (%) n=140
Fever grade				
High grade	6 (25.0)	9 (7.8)	0.013	15 (10.7)
Low and moderate grade	18 (75.0)	107 (92.2)		125 (89.3)

Clinical predictors of Bacteraemia

Each day increase in the duration of fever was associated with a 14% increase in the odds for Bacteraemia (AOR 1.14, 95% CI -1.02 to 1.27, Table 3). Participants who were admitted with lethargy were 6.5 times more likely to have bacteraemia (AOR -6.46, 95%CI -1.27 to 32.80, Table 3). Those admitted as in-patients were also thrice likely to have bacteraemia when compared to out-patients (AOR -3.66 95% CI -1.11 to 12.08, Table 3).

Table3: Risk predictors for Bacteraemia.

Variables	Adjusted odds ratios and 95% confidence interval	P-value
Duration of fever	1.14 (1.02 to 1.27)	0.02
Lethargy		
Yes	6.46 (1.27 to 32.80)	0.02
No	1.00	
Hospitalization		
Yes	3.66 (1.11 to 12.08)	0.03
No	1.00	
Tachypnoea		
Yes	6.53 (1.90 to 22.46)	0.003
No	1.00	
Lymphopenia		
Yes	4.19 (1.24 to 14.14)	0.02
No	1.00	

DISCUSSION

We investigated the burden and factors predictive of bacteraemia among under-five children with acute undifferentiated fever seen at the emergency unit in North-western Nigeria. We found that one in six participants had bacteraemia, majority from gram negative enteric pathogens. Inpatient care, longer duration of fever, lethargy, tachypnoea and lymphopenia were all associated with the increased odds of bacteraemia.

The prevalence of bacteraemia among under-five children with acute undifferentiated fever was 17.1%. This is similar to the rate reported among children with similar characteristics in Benin, Nigeria. [5] However, a higher prevalence rate (25.7%) was reported among Indian children.[25] The diagnosis of bacteraemia in the current study was based only on blood culture as opposed to the Indian study where the Widal test, a serologic test fraught with high false positive rates complemented blood culture in the diagnosis of Salmonella infection, this may have over-estimated the burden of bacteraemia.[26] In contrast, the prevalence of bacteraemia was significantly lower (1.4%) in a previous study conducted in Brazil among similar study population to ours.[27] The higher positive culture rate found in our study could be because of the utilization of a more sensitive automated culturing system unlike the Brazilian study where the conventional manual bacteriological culture method was used.

Gram-negative pathogens were the predominant cause of bacteraemia among our cohort, accounting for over 80% of the isolates. The preponderance of gram-negative pathogens in childhood bacteraemia had been described previously in Northern Nigeria and in other Low-Middle income countries. [5,7,25,28] The preponderance of enteric gram-negative pathogens in the study location, like in most resource-poor settings could be related to the high presence of predisposing factors such as high level of poverty, limited access to clean water, poor sanitation and malnutrition.[29] In contrast, some studies have reported predominantly gram-positive pathogens especially Staphylococcus aureus among febrile children.[30-32] While this difference might reflect geographical variations of bloodstream bacterial pathogens, the characteristics of the study participants and the study design could also account for the differences in the organisms isolated. The current study is prospective hence, very minimal selection bias unlike the previous studies which were retrospective in design. Also, our subjects are those with acute undifferentiated febrile illnesses and are also devoid of peculiar risk factors such as HIV infection that could predispose to Staphylococcus aureus infection. [33]

Salmonella infection accounted for most of the cases consistent with the previous reports from the same study location. [28,34] Bacteraemia caused by Salmonella is most prevalent in the dry season (October–March) and the conduct of the present study during this peak period may have accounted for the predominance of the organism.[28] Meningococcal bacteraemia was not found in the current study despite the timing of the study which coincided with the seasonal peak of Neisseria Meningitides. This observation may, however, not reflect the burden of meningococcal bacteraemia in the study location because subjects with overt clinical features of meningitis such as neck stiffness and abnormal tone were excluded from the current study.

In vitro antibiotic susceptibility testing revealed a high prevalence of Co-trimoxazole resistance especially by Salmonella infection but with high sensitivity to gentamicin, ciprofloxacin, ceftriaxone and augmentin. A previous multicenter study in Northern Nigeria has also shown high resistance of non typhoidal Salmonella and Salmonella Typhi to co trimoxazole. [28] This finding has some implications; first, augmentin would seem a rational antibiotic on out-patient basis but it is quite expensive compared to co-trimoxazole. Second, ciprofloxacin is cheap and available in both oral and parenteral forms and could be used in both in and out-patient settings but the widespread use of ciprofloxacin has been associated with a high incidence of extended-spectrum β-lactamase enzymeproducing pathogen hence increasing antibiotic resistance.[35] Third, like ciprofloxacin, ceftriaxone is a broad-spectrum antibiotics and its use as a first-line drug could also promote resistance. Also, it is expensive and available only in a parenteral formulation and would be less affordable in resource-poor settings where the majority have no form of health insurance.

In this study, the duration of fever rather than the degree of fever was associated with increased odds of bacteraemia with each day increase in the duration of fever associated with a 14% increase in the odds for bacteraemia, and this is similar to a previous study.[36] Other studies have also failed to demonstrate a correlation between the degree of fever and positive bacterial

culture.[37,38] Fever results from a cytokine-mediated elevation of the hypothalamic set point and is perhaps the earliest systemic feature of microbial invasion of the bloodstream.[39] An increasing duration of fever could therefore reflect an intense bacterial multiplication and an increased tendency of positive culture as obtained in our study. Furthermore, participants that required hospitalization were thrice likely to have bacteraemia when compared to out-patients while those admitted with lethargy and fast breathing were 6.5 times more likely to have bacteraemia, and this is consistent with a previous study.[27] Febrile children presenting with lethargy and fast breathing often appear ill, necessitating in-patient care. In this study, a subjective assessment of "ill/toxic look" made by the attending emergency clinician was the eligibility criteria for hospitalization; the discriminatory power of the criteria thus gave it credibility and could thus be adopted in triaging febrile children in other resource-poor settings where facilities and resources for in-patient care are suboptimal.

Among all haematological parameters, a low lymphocyte count remained predictive of bacteraemia and participants with lymphopenia were four times likely to have bacteraemia compared to those who did not have lymphopenia. This finding could be due to the predominance of Salmonella species among the organisms isolated. Previous studies, including controlled human infection model have consistently demonstrated association between Salmonella infections and lymphopenia have been demonstrated in previous report. [40, 41]

STRENGTHS AND LIMITATIONS

We have described the burden and the predictors of bacteraemia among under-five children with acute undifferentiated fever. Such children pose a diagnostic challenge and clinicians are often in a dilemma whether to use antibiotics empirically or not, unlike previous studies on bacteraemia conducted among children with focal signs of infection e.g., meningitis, pneumonia, in whom the deployment of empirical antibiotics is justified. In addition, our study design was prospective and this enabled the recruitment and the collection of data from all our participants using pre-set clinical criteria thus, minimising selection bias as observed in a previous study. [7]

However, about 13% of the study participants were lost to follow-up and hence the mortality rate as presented may not reflect the actual death attributable to bacteraemia among the study participants. In addition, the potential impact of the pathogens causing bacteraemia on the identified predictors could not be assessed due to preponderance of Salmonella amongst the isolates. Therefore, this picture may not apply in other settings where pneumococcal or other forms of bacteraemia is most prevalent

CONCLUSIONS

We have shown that one in six under-five children presenting to a typical emergency unit in North-western Nigeria with AUF had bacteraemia and this was mainly due to Salmonella. Participants who required hospitalization, those that presented with lethargy, had fever beyond seven days, had tachypnoea or had lymphocytes counts <3 x 109/L was at increased odds of bacteraemia. We therefore, recommend that in settings similar to ours, the presence of these clinical predictors could form the basis for a rational ordering of blood culture. Also, where facilities for blood cultures are not available, febrile under-five without focal signs but possessing the highlighted clinical features should be treated empirically for bacteraemia using the most sensitive antibiotics.

DECLARATIONS

Authors' contributions

TOO, TOA, KSE conceived the study; TOO, TOA, KSE, FH designed the study protocol; TOO recruited and obtained clinical data; AI analysed the data; TOO and AI prepared the first draft of the manuscript. All authors contributed to the first major revision of the manuscript, final manuscript revisions, and approval of the final version. TOO, RO and SO are guarantors for the paper.

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Ethical Approval and consent to participate

This was a sub-study under a the parent study – Community acquired Pneumonia and invasive Bacterial Disease with ethical clearance by the ethics committees of the University of Nebraska Medical Center, Aminu Kano Teaching Hospital and the Kano State Hospital Management Board. Parents or guardians provided informed consent for participation of their wards in the study.

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