Journal of Advances in Medicine and Medical Research

25(4): 1-9, 2018; Article no.JAMMR.38781
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Retrospective Analysis of Malarial Parasitemia and Bacteremia in Febrile Episodes Seen at Tertiary Hospital at Nguru, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author KOO designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MYB and BAZ managed the analyses of the study. Authors SP, STB, RTA and JOO managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2018/38781
Editor(s):
(1) Rodrigo Crespo Mosca, Department of Biotechnology, Institute of Energetic and Nuclear Research (IPEN-CNEN), University of Sao Paulo (USP), Brazil.
Reviewers:
(1) Judith Lum Ndamukong Nyanga, Higher Teachers Training College, University of Yaounde I, Cameroon.
(2) Kamgain Mawabo Lugarde, District Hospital of Deido, Cameroon.
(3) Norma-Aurea Rangel-Vazquez, Mexico.
Complete Peer review History: http://www.sciencedomain.org/review-history/23185

Original Research Article

Received 13th November 2017
Accepted 7th February 2018
Published 14th February 2018

ABSTRACT

Background: Febrile episode remains the common clinical presentation responsible for hospital admission among children aged less than 5 years in sub-Saharan African. The overlapping of clinical signs and symptoms, with diverse aetiological agents implicated in febrile illness, tends to compound effective diagnosis and management approach in a low-resource healthcare setting.
Objective: We retrospectively analysed malaria parasitemia and bacteremia results of febrile patients seen at a tertiary hospital in Nguru, Yobe state, Nigeria.

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Study Design: A retrospective study analysed malarial parasitemia and bacteremia of febrile patients aged less than 12 years.
Place and Duration of Study: The study was conducted at the federal Medical center Nguru in the department of Medical Microbiology and Paediatric that spanned between January and December 2014.
Methodology: Thick and thin blood smear examination for asexual malarial parasite, blood culture technique for bacterial pathogens isolation, and antibiotic susceptibility testing were employed for the study.
Results: Malarial parasitemia was detected in 44(32.6%) cases, bacterial pathogens isolated in 51(37.8%) and co-infection prevalence of 16.3% respectively. Five different bacterial pathogens were isolated, *Staphylococcus aureus* accounted for 34(66.9%), *Salmonella* spp 10(19.6%), *Escherichia coli* 4(7.8%), Coliforms 2(3.9%) and *Streprotococcus pneumoniae* 1(2.0%) respectively. The significant statistical difference was observed between clinical details and microbiological indices, malarial parasite ($P<0.001$) and bacterial pathogens ($P<0.0001$). High malarial parasitemia and bacteremia was observed within the age-group of 1-11 months and >60 months. The bacterial pathogens demonstrated high resistance pattern to ampicillin and cotrimoxazole.
Conclusion: These findings presented local epidemiological data of febrile episode that could optimized febrile illness diagnosis and management approach.

Keywords: Febrile illness; malarial parastemia; bacteremia, Nguru.

1. INTRODUCTION

Febrile episode remains the common clinical presentation responsible for hospital admission among children aged less than 5 years in sub-Saharan African, which is associated with high morbidity and mortality rate [1,2]. Clinically, it is characterized by increased auxiliary temperature (>38°C) and different subclinical presentations. In malaria endemic regions, febrile illness is often associated with malaria, often responsible for overdiagnosis of malaria and inappropriate prescription/administration of antimalarial drugs, even in cases with negative blood smear result. Malarial disease accounts for 16 million admission and high mortality of appropriately 4.6 milliion of children aged less than 5 years [3]. Nigeria, is one of the malaria endemic countries in sub-Saharan Africa, with the malaria transmission maintained by ecological factors that encourage the breeding of *Anopheles* mosquitoes in the communities. According to the Nigeria Centre for Disease Control 2012 [4] malarial surveillance studies reported malarial incidence of 50.2%, while higher malaria prevalence was reported in other studies conducted in Nigeria and some sub-Saharan African countries [5,6-10]. In contrast, lower prevalence in some region of sub-Saharan Africa [10-12] that may be attributable to WHO initiatives on malarial public health awareness and prevention.

Decline in malaria incidence as documented in most some studies, and non-responsiveness of febrile patients to antimalarial therapy, thus raises the possibility of other non-malarial aetiological agents/or coinfection of malarial and bacteremia as contributory factors of febrile illness. Clinical implication of malarial and bacteremia as predisposing risk factor for febrile illness have been well documented [1,10,11-14]. However, in malarial endemic region, invasive bacteremia due to Non-typhoidal Salmonella spp predispose to malaria, dependent on the geographical location, seasonal and climatic pattern, socio-demographical variables and comorbdities- urinary tract infection, acute respiratory tract infection, HIV/AIDS, malnutrition and typhoid fever [14,15,16] Wide ranged of bacterial pathogens from enteric gram-negative Enterobactericaea, to gram-positive bacteria has been implicated in febrile episode [6,9,10-21]. Non-malarial agents associated with febrile illness such as brucellosis, leptosporosis, salmonellosis are emerging in region with high livestock population and poor sanitation [12,13].

As malaria and bacterial pathogens resistant strains continued to increase due to selective presssure, empirical therapy in the treatment and management of febrile illness without laboratory report contribution cannot be ruled out. As antimalarial drugs are still being prescribed in cases of negative malarial test/ or where no laboratory test carried out. Similar practise is common with the prescription of broad spectrum antibiotic in suspected bacteremia. Because of the non-definitive symptology and diverse aetiological agents of febrile illness, effective

diagnosis and management in low-resource setting may be difficult. Therefore, diagnostic indices derivable from retrospective analysis such as this study, tends to provide local epidemiological data that could optimize patient management based on available facilities and complement the standardized treatment guidelines. Therefore, we retrospectively evaluated the implication of malaria parasitemia and bacteremia in the diagnosis of febrile patients seen at a terttary hospital in Nguru, Yobe state Nigeria.

2. METHODOLOGY

2.1 Study Site

The retrospective study was conducted at the department of medical microbiology, Federal Medical centre, Nguru, between January and December 2014. The hospital is a 250 bed capacity, which provides multimedical specialties to Nigerians and citizens of neighboring republics of Niger and Chad. Nguru is located in the desert region of one of the administrative state in the northeastern Nigeria, Yobe state boarded by Chad and Niger republic. Geographically, it is located on latitude 12'52'45°N and longititute 10' 27'09°E, with a land mass of 912 km^2, with population of 150,632 according to 2006 Nigeria census. The town is transverse by Hadejia-Nguru wetland that is used for irrigation and fishing. This environmental ecology support inbreeding of mosquites and transmission of malarial infections. The settlement is a mixture of old and modern structural settlement and domestication of ruminant animals for economic purposes.

Criteria of inclusion, malarial parasite and blood culture results of febrile patient aged less than 12 years old seen at the pediatrics clinic, with other information- age, gender, associated clnical details and antibiotic susceptibility pattern were extracted and analysed. A total of 135 patients were included in the study

Laboratory analysis: Thick and thin blood smears were made and stained by Giemsa stains and examined microscopically. Asexual malarial parasite seen in the blood film confirmed malarial infection. 2-3 ml of venous blood was collected aseptically, and dispensed into the 2 blood culture bottles containg Robertson's cooked meats, incubated at 37°C. The bottles were examined daily for turbdity indication of bacterial growth and subcultured onto blood and MacConkey agar plates and incubated at 37°C. Suscepted bacterial colonies were identified by standard bacteriological methods [22]. The bottles were considered as negative and discarded if there was no indication of bacterial growth after 7 days of incubation. Antibiotic susceptibility testing of the bacterial isolates was carried out by disc diffusion method according to CSLI guideline on Mueller-Hinton agar [23]. The same antibiotic discs tested within the study period were documented which included the following, ampicillin, ciprofloxacin, ofloxacin, gentamycin, rifamipicin, cotrimoxazole, erythromycin and augmentine. Demographic and microbiological data were analysed using SPSS version 17.0, values were expressed as frequency and percentages. Catergorical variables were compared by chi-square test, with significant difference at $p<0.05$.

3. RESULTS

Microbiological and clinical data of 135 febrile children were extracted, analysed and presented on Table 1, gender distribution showed 75(55.6%) males and 60(44.4%) females, with male to female ratio of 1:1.25, The mean age of 11.5±10.2 months, and age group distribution of <1 month 16(11.9), 1-11 months 39(28.9), 12-35 months 17(12.6), 36-59 month 14(10.40) and 60-144 month 49(36.3). Clinical conditions associated with febrile episodes- fever, neonatal sepsis and sepsis with the following frequency of occurrence, 71(52.6), 19(14.1) and 17(12.6) respectively. *Plasmodium falciparium* parasite was detected in 44(32.6%) cases, bacterial pathogens isolated in 51(37.8%) cases and co-infection in 22(16,3%) cases. Five different bacterial pathogens were isolated, *Staphylococcus aureus* was isolated in 34(66.9) cases, *Salmonella spp* in 10(19.6), *Escherichia coli* in 4(7.8), Coliforms in 2(3.9) and 1(2.0) in *Strep. pneumoniae* respectively. High frequency of *Plasmodium falciparium* bacteria pathogens, and coinfection were recorded in the following clinical details, fever, neonatal sepsis, sepsis and rashes, in which *S. aureus* predominate 21(61.7%), 6(17.6), 4(11.8), 3(8.8), *Salmonella* spp 7(70.0) and 2 Coliforms isolates and *E.coli* 3(75.0) respectively. In other clinical details, 3 *Salmonella* spp isolates from Enteric fever and sickle cell anaemia, one *Streptococcus pneumoniae* isolate from bronchopneumonia, and one *E. coli* isolate from genital mutilation case.

Association was observed between the clinical details and microbiological data, malarial parasite

(P<0.001) and bacterial pathogens (P<0.0001) as presented in Table 2. Table 3 presented the microbiological data versus the age-group of the children, 61% of bacterial pathogens isolated were from children aged less than 2 years compared to 39.2% from children greater than 2 years, and *S. aureus* isolates predominate in all the age-group. The antimicrobial susceptibility pattern of the bacterial pathogens tested as presented in Fig 2, high susceptibility was demonstrated to erythromycin, ofloxacin, ciprofloxacin (8.8%), gentamycin (8.8%-25%), rifampicin (8.8%) and augmentine (2.9%-25%), moderate susceptibility to amoxicillin (25%-44%), and high resistance to cotrimoxazole (70-100%) and ampicillin (75%-100%) respectively.

Table 1. Demographic and microbiological characteristics of the patients

Demographic variables	Frequency (%)
Age-group	
<1month	16(11.9)
1-11	39(28.9)
12-35	17(12.6)
36-59	14(10.4)
60-144	49(36.3)
Gender	
Male	75(55.6)
Female	60(44.4)
Clinical details	
Fever	71(52.6)
Neonatal sepsis	19(14.1)
Sepsis	17(12.6)
Enteric fever	5(3.8)
Abdominal pain	9(6.7)
Bronchopneumonia	1(0.7)
Filarisis	1(0.7)
Recurrent rashes	7(5.2)
Sickle cell anemia	2(1.5)
Acute osteomyelitis	1(0.7)
Tetanus	1(0.7)
Co-infection	22(15.6)
Genital mutilation	1(0.7)
Microbiological data	
Malarial	44(32.6)
Bacteremia	51(37.8)

4. DISCUSSION

In this study, malarial parasitemia was detected in 44(34.7%) cases, bacterial pathogens isolated in 51(34.3%) cases and co-infection in 2 2(13.6%). There was neither malarial parasite nor bacterial pathogens detected in 65% of febrile cases, consistent with other studies and affirmed that other aetiological agents are capable of eliciting febrile illness. In geographical location with high livestock population and pastoralist activities, zoonotic pathogens like Brucella spp, leptosporosis have been implicated in febrile illness [12,13]. Clinically, association between febrile illness and comorbdities like urinary tract infection, respiratory tract infection, gastroenteritis, age malnutrition, anaemia and HIV/AIDS had been well documented [8,11,12,15-18].

Malarial parasitemia rate of 34.7% recorded in this study can be considered low, when compared with similar studies with higher rate (>40%) [4,6,8,9], and lower prevalence level of 1.6% [11] and 8.9% [12]. We are of the opinion that the environmental ecology of Nguru should support higher malaria parasitemia level, as it support *Anopheles* mosquito breeding and transmission of malarial diseases. However, the observed prevalence in our study may be due to other factors such as, (i) pre-medication practice before presentation at the hospital which is a common norm (ii) severity of infection and the level of parasite density and (iii) the competence and skill of the personnel involved in staining and examination of the blood smear could contribute to low prevalence. The severity and outcome of febrile illness is known to be influenced by socio-demographic variables - age, gender and comorbdities Age as predisposing factor of febrile illness, has been well documented [17,18], as observed in our study high numbers of cases were within the aged less than 2 years.

Malaria and bacteremia co-infection is common clinical presentation among children aged less than 2 years, with clinical presentation like meningitis, pneumonia, and septicemia responsible for high morbidity and mortality rate [14]. The bacterial pathogen isolation rate of 32.6% is comparable to 34% reported in Nigeria [9], and 32% in Tanzania [13] but higher than 9.8% reported in Tanzania [11], 11.4% in Tanzania [6], 3.2% [12] and 19.8% in Ghana [20]. Bacterial pathogens implicated in febrile episode varies with geographical location, age, severity of infection and subclinical condition [14]. Generally, members of Enterobactericeae, *Staphylococcus* spp, and *Salmonella* spp (NTS and typhi) are the leading pathogens [14], but *Streptococcus pneumoniae* accounts for most pathogens in children aged less than 2 year [24-27], while in malaria endemic region, like West Africa, NTS remains the predominant pathogen

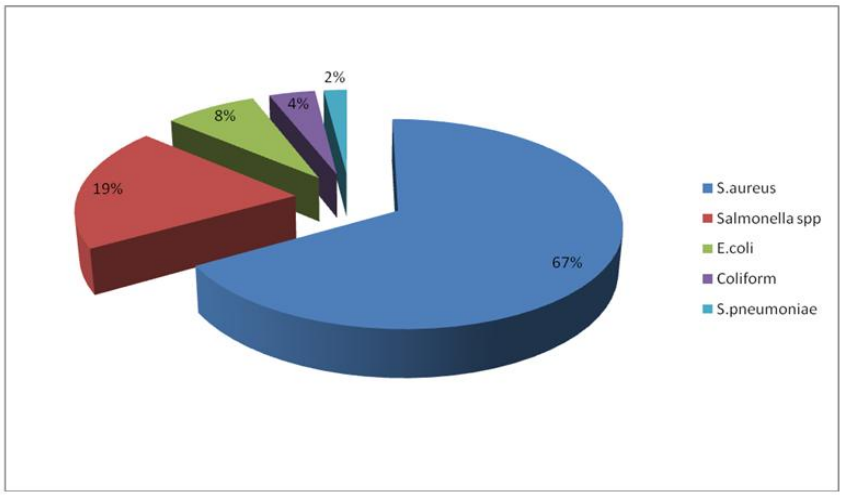

Fig. 1. Frequency of bacterial pathogens isolated

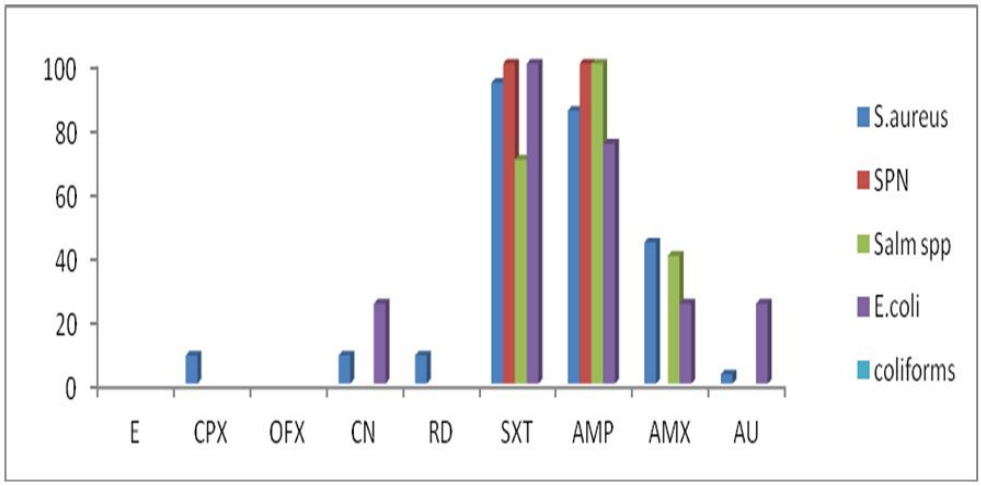

Fig. 2. Resistance pattern of bacterial pathogens tested

that can precipitate malaria disease in most cases [15]. In our study, *S. aureus* accounted for 66.7% of the total pathogens isolated, which is consistent with other studies [19,21,25], followed by *Salmonella* spp (19.6%), *E. coli* (7.8%), Coliforms (3.9%) and *Steptococcus pneumoniae* 2.0%. However, the observed variation in the bacterial pathogens isolation is known to be influenced by socio-demographic variables, microbiological and clinical indices. Therefore, we compared the clinical details and microbiological data, and it revealed association between clinical details and microbiological data [malarial parasite ($P<0.001$) and bacterial pathogens ($P<0.0001$), a clinically useful information necessary to initiate empirical therapy in any febrile illness.

Salmonella spp (typhi and non-typhoidal) is one of the leading bacterial pathogen associated with malarial infection, and responsible for high morbidity and mortality among children [15]. Of the 10 *Salmonella* spp isolates, co-infection was recorded in 7of the feverish cases, 2 in sickle cell disease cases and 1 in enteric fever. In a study conducted in UK, Barkin et al. [28], observed that febrile children with sickle cell disease(SCD) has a 3-5% risk of developing bacteremia due to the compromise immune function, and reported bacteremia prevalence of 0,8% of 1118 SCD cases studied. A meta-analysis of bacterial ostemyelitis in SCD in Africa, Thanin et al. [29] reported a prevalence of 45.9%. While 2 *Salmonella* spp isolates were recovered from the 3 SCD patients in our study.

Table 2. Clinical details versus microbiological data of the patients

Clinical details	Malaria(44)	Bacteremia(51)	Co-infection(21)	S.aureus(34)	Salmonella spp(10)	E.coli(4)	SPN(1)	Coliform(1)
Fever(n=71)	29(65.9)	32(62.7)	15(71.4)	21(61.7)	7(70)	3(75)		1
Neonatal sepsis(n=19)	3(6.8)	6(11.8)	1(4.7)	6(17.6)				
Sepsis(n=17)	3(6.8)	5(9.8)		4(11.8)				1
Enteric fever(n=5)		1(2.0)			1(10)			
Abdominal Pain								
Bronchopneumonia(n=1)	1(2.3)	1(2.0)	1(4.7)				1	
Filariasis(n=1)								
Rashes(n=7)	6(13.6)	3(5.8)	3(14.3)	3(8.8)				
Sickle cell anaemia(n=2)		2(3.9)			2(20)			
Osteomyelitis(n=1)	1(2.3)							
Tetanus(n=1)								
Genital mutilation(n=1)	1(2.3)	1(2.0)	1(4.7)			1(25)		

p-value, Clinical details versus malarial parasite=P< 0.001, Blood culture=P<0.79, Co-infection=P<0.059, Bacterial pathogens=P<0.0001

Table 3. Microbiological data versus the age-group of the patients

Microbiological data	<1mth	1-11mth	12-35mth	36-59m	>60mth
Malarial parasite	3	13	9	5	14
Blood culture	4	22	5	5	34
Co-infection	-	8	3	3	8
S.aureus	4	16	4	2	8
Salmonellaspp		2		3	5
E.coli		2	1		1
S.pneumoniae		1			
Coliforms		1			1

Acute respiratory tract infection, is a common clinical condition associated with febrile illness, particularly in children less than 2 years [24,26]. In this study, the only Strep. *Pneumoniae* isolate was recovered from a patient with a case of bronchopneumonia, in contrast to SPN as a leading pathogen in a study conducted in Mozambique that accounted for 34% [22,24]. Factors that may be responsible for the low SPN isolation rate are, possible overgrowth by other bacterial pathogen or the fastidious nature of the pathogen. *E. coli* is the leading pathogens implicated in urinary tract infection, a comorbdity in febrile episodes [6,19]. Three of the 4 *E. coli* isolates were recovered from patients with malarial fever, which futhered affirmed the malaria, UTI implication in febrile illness. Malaria and bacteremia coinfection posed a serious clinical challenge capable of blurring prompt diagnosis, treatment and management approach. Clinical implication of the coinfection and febrile illness has been a topic of clinical debate, as some studies had reported that bacteremia infection could predispose, or aggravate the course of acute febrile illness, depending on the infecting bacteria pathogens, or whether there is focus / or no focus of infection [6], and immune status of the patient. Several studies have linked the susceptibility to immune status, role of mediators and immune activation impact of parasite density and severity of febrile illness [30,31]. Because of such possible scenario, peadiatrician practicing in poor resource health care setting tends to prescribed a combination of antimalarial and broad spectrum antimicrobial to address possible underlying bacterial infection while awaiting the blood culture results, if it is avaliable. A meta-analysis review of acute febrile episodes in sub-Saharan Arica, co-infection rate range of 4.0- 9.4% was reported [14], while higher rate of 40% in Kenya [13] and 45% in Tanzania [12], compared to 12.5% is documented in our study. Several factors such as the geographic location, environmental ecology, severity of infection, co-morbidities like malnutrition, HIV/AIDS may be responsible for difference in coinfection rate.

As antimicrobial resistance phenomenon continued to increase globally, the practice of misdiagnosis and administration of antimicrobial agents even in cases of negative malarial result and empirical approach, these are some of the factors fuelling the phenomenon in Africa. At the community level, self-medication of commonly avalaible and affordable agents remains is a common norm, which is always the firstline medical attention, in unresponsiveness cases the hospital becomes the last option. The practise had impacted negatively on the increasing resistance pattern of bacterial pathogens tested in the laboratory. The antimicrobial susceptibility pattern demonstrated by the bacterial isolates tested revealed high susceptibility to olfoxacin, erythromycin, ciprofloxacin (8.8%) rifamipicin (8.8%), gentamycin (8.8-25%) and augmentine (2.9-25%), Moderate susceptibility to amoyxicillin (25-44%) and high resistance to cotrimoxazole (70-1005) and ampicillin (75-1005). The high resistance pattern recorded with cotrimoxazole and ampicillin, have been recorded in other studies [6,12,19], which highlight the over usage of these agents. Apart from erythromycin, gentamycin and augmenine, that are routinely prescribed and administered for peadiatrics , the other agents tested are seldomly administered because of their clinical contradictions. This pattern advance the need for synergy between the laboratory and pediatrics department in developing a drug policy and those to be tested for clinical purposes.

Though, it is a retrospective study, but the findings have provided an epidemiological picture of malaria parasitemia and bacteremia in febrile episode. Limitations in this study which includes, documentation errors and bias associated with respective study, the number of patient data is few and duration of the study is rather short, to serve as good representation of febrile illness episode assessment and draw conclusion other

important demographic variables like seasonal pattern and stratification of febrile illness into either severe or non-severe were not documented, and serotyping of some bacterial pathogens (*Salmonella spp, E. coli*) were not carried for better evaluation.

5. CONCLUSION

The clinical and microbiological indices shed light on febrile episodes in the study area, that could be served as template for more comprehensive studies that may look into non-malarial aetiological agents and effect of other demographic variables like seasonal pattern and populace occupation.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study was approved by the Institution Review Board.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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