Bacterio-clinical Characteristics of Pathogens Isolated from Febrile Children in Lagos, Nigeria

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Abstract

Febrile illness is a broad clinical term, generally considered to be caused by pathogens and characterized by fever.There are myriad of infectious agents that trigger fever. While acute febrile illness cases in Africa are often attributed to malaria or viral infections,bacterial, fungal, and other parasitic causes exist. A total of 660 venous Blood and mid-stream urine samples were collected from study participants with acute fever ≥ 37.5^{o}C from May to November, 2024 and analyzed at Nigerian Institute of Medical Research, Lagos.The participants were recruited from Primary Health Centres (PHCs) in the 3 senatorial district of Lagos covering Alimosho, Surulere and Ikorodu LGA. Bacterial isolates were identified using Microbact^{tm}gnb 24E test system. Sociodemographic and metadata of participants were also assessed. Pathogenic bacteria were detected in 9.6 % (63 of 660) and characterized into bacteremia with urinary tract infections (UTIs) (65% :41 of 63), bacteremia (27%), UTIs (8%). The highest number of participants having bacteremia with UTI were from Ikorodu (56% :23 of 41), Alimosho (27%), and Surulere (17%).The commonest pathogen found in all sites was *Escherichia coli* (35%:22 of 63). Species of *Acinetobacter spp*, *Klebsiella spp,* Citrobacter spp, *Enterobacter spp*, *Stenotrophoma spp* and *Averyella spp* were also isolated. Participants primary source of drinking water was borehole (77%). Low haemoglobin level (< 10g/dl) was found in 66% of all the participants and in 79% of participants with pathogens. Diagnosing children with febrile illness of bacterial etiology unveiled a diversity of other causes of fever in under-5 children.

Keywords: Bacterio-clinical characteristics, Pathogens isolated and Febrile children

Introduction

Fever is usually the first sign in children's illness with or without accompanying symptoms (Wright & Auwaerter, 2020,& Steel et al, 2018). It is clinically referred to as febrile illness cause by an infectious agents (Rhee et al, 2019, Abade et al, 2018, Panzner et al, 2016). In low- and middle-income countries especially those in Africa, up to 80% of children who visit a healthcare facility present with an acute febrile illness (AFI) (Marks et al, 2021, Ombelet et al, 2019,Von Kalckreuth et al, 2016, Herlihy et al, 2016). Malaria is mostly attributed to fever in Africa even though bacterial, fungal, and parasitic causes exist (Shrestha et al, 2020 & Marks et al, 2021). The prevalence of urinary tract infections (UTIs) is greater in infants with temperatures ≥ 39°C than those with temperatures < 39□ (Daniel et al, 2023). Due to economic constraints, most diagnosis are narrowed to exclude these possible causes (Aigheyisi & Edore, 2019).

In Nigeria, children below the age of 14 years constituted more than 40% of the population (GBD, 2018) while children aged five years and below constitute the bulk of patients attending the pediatrics out-patient clinics (Iroh et al, 2016, GBD, 2018, & Maze et al, 2018).These age groups are particularly vulnerable to many communicable and infectious diseases, and mortality among them is usually very high (Masoud, 2021 & Tekgul et al, 2020). Four of those pathogens; *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*, increased the number of deaths globally by at least four times in 2019 alone, reaching over 670,000 (WHO,2021). Nigeria has the fifth-highest under-five mortality rate in the world, with 117 deaths per 1000 live births backdated from 2019, and recently the second highest globally (UNICEF, 2019 & Punch Newspaper, 2024).

The most common bacterial infection in childhood is urinary tract infection (La Scola et al, 2018, Atay et al, 2021). Nearly 7.8 percent of children under the age of nineteen years are exposed to bacterial urinary tract infections globally (Tullus & Shaikh, 2020). About 30% of infants and children experience recurrent infections after the initial UTI with varieties of symptoms (Roberts & Wald, 2018, Ammenti et al, 2023). The incidence of UTIs depends on age and sex. The prevalence is higher in males than females (4:2) in the first year of life (Alberici et al, 2019, Tullus & Shaikh, 2020). Most infections are caused by *Escherichia coli*, although in the first year of life *Klebsiella pneumoniae* , *Enterobacter spp* , *Enterococcus spp* and *Pseudomonas spp* are more frequent than later in life, and there is a higher risk of urosepsis compared with adulthood (Stocker et al, 2021, Olorukooba et al, 2020).

The risks associated with urinary tract infections may be classified into cystitis and pylonephritis involving the lower and upper urinary tracts respectively. Cystitis (lower urinary tract) is inflammation of the urinary bladder mucosa with symptoms including dysuria, stranguria, frequency, urgency, malodorous urine, incontinence, haematuria, and suprapubic pain (Swerkerson et al, 2016) . Pyelonephritis (upper urinary tract) is diffuse pyogenic infection of the renal pelvis and parenchyma with symptoms including fever (Swerkerson et al, 2016).Young children may have nonspecific signs which are rarely diagnosed accurately unlike adults. These children may present with symptoms such as poor appetite, failure to thrive, lethargy, irritability, vomiting, or diarrhoea (Marks et al, 2021 & Tullus & Shaikh, 2020). Bacteremia is another risk associated with UTIs and can progress to sepsis when immune system is weakened (Alemnew et al, 2020, Hercik et al, 2018, Stein et al, 2015).

In this study investigations were done to detect the presence of bacterial pathogens in blood and urine specimens collected from under-5 aged children attending selected primary health centres (PHCs) in Lagos state. Bacterial isolates were Identified using Microbact^{tm} gnb 24e test system and classified into three clinical groups.The characterization of bacterial pathogens into those causing bacteremia, UTIs, and UTIs plus bacteremia gave additional insights into the etiology and risks associated with febrile illness in little children.

Methods

Laboratory analyses were carried out on the venous blood and mid-stream urine samples collected from febrile under-5 aged children attending selected primary health care facilities in Lagos. The PHCs are located in Alimosho, Surulere and Ikorodu L.G.A being Lagos West, Central, and East senatorial district respectively. The recruited primary health care facilities (Meiran, Akowonjo, Ikotun, Orile-Iganmu, and Igbogbo PHCs) are public institutions providing comprehensive medical care to patients of all ages in Lagos state.

A minimum of 220 subjects from each L.G.A, with a total of 660 participants in all the sites,were recruited with written informed consent from their caregivers/ parents. The inclusion criteria were under-5 aged children with fever (≧ 37.5°C), who tested negative for malaria infection and were residence in the study area.The study focused on bacterial pathogens isolated from these febrile children and grouped them into those causing bacteremia with UTIs, only bacteremia, and only UTIs. Clinical examination and questionnaire were employed to obtain sociodemographic data and other information such as source of drinking water and caregivers' knowledge febrile illness.
All laboratory tests were carried out at Nigerian Institute of Medical Research (NIMR), Lagos, including complete blood count, urinalysis, blood and urine culture. Identification of bacterial isolates from urine and blood cultures was done using Microbact ^{tm} gnb24E bacterial identification test system. Ethical approval (IRB/23/098) for this study was obtained from the Health Research, Ethics committee, of Nigerian Institute of Medical Research (NIMR), Lagos. Administrative approval and permission was further obtained from the Lagos State Primary Health Care Board.

Statistical Analyses

Analyses were performed using Statistical Package for the Social Sciences (SPSS) version 26. Normal growth (height) for age and sex were generated using WHO growth standards (Marks et al, 2021, Abade et al, 2018) and body temperature was calculated by taking the axillary temperature measurement (Marks et al, 2021, Elven et al, 2020). A clean voided midstream urine sample was collected after cleaning the external genitalia. Urinary tract infection was excluded following the guidelines of European Association of Urology (EAU)/European Society for Paediatric Urology (ESPU). Urinary tract infection was excluded if the dipstick was negative for both leukocyte esterase and nitrite or microscopic analysis was negative for both pyuria and bactereriuria (Hay et al, 2016, Tullus and Shaikh, 2020). The classical definition of $>10^5$ CFU/mL of voided urine was still used to define significant UTI (Stocker et al, 2021, Liu et al, 2016).

Results:

Table1: Characteristics of participants by study sites

Characteristics of Participants	**ALIMOSHO**	**SURULERE**	**IKORODU**	**TOTAL**
Mean age	3.5	3.9	3.2	
Total No. Males	77 (35%)	88(40%)	106 (48%)	271 (41%)
Infected Males	7(23%)	7(23%)	16 (54%)	30(48%)
Total : Females	143 (65%)	132 (60%)	114 (52%)	389 (59%)
Infected Females	13 (39%)	5 (15%)	15 (46%)	33 (52%) Total No. Infected: 63 (9.6%:63 of 660)
Water Source:				
Borehole	166 (75%)	202(92%)	143(65%)	511 (77%)
Others	54 (25%)	18 (8%)	77 (35%)	149 (23%)

Caregiver Knowledge: Febrile illness	154 (70%)	143 (65%)	136 (62%)	433 (66%)
Common Symptoms	Fever,cough, weakness, Loss of appetite, vomiting, urinary irritation, diarrhoea.	Fever,cough, weakness, abdominal pain, Loss of appetite, vomiting, urinary irritation, diarrhoea.	Fever,cough, weakness, vomiting, urinary irritation, diarrhoea.	Low Hb level in most of the Participants Hb<10g/dl : 436 (66%: 436 of 660)
Number with Leucocyturia	14(14 0f 63: 22%)	8(8 of 63:13%)	23 (23 of 63: 37%)	45(71%)
No. with urine Nitrite	11(11 of 63: 17%)	6 (6 of 63:10%)	20(20 of 63: 32%)	37 (59%)
No. with HB<10g/dl	15(15 of 63:24%)	9(9 of 63:14%)	26(26 of 63: 41%)	50 (79%)
No. with Bacteremia with UTI: Bacteremia only UTI only	12(19%) 6 (10%) 3 (5%)	7(11%) 4 (6%) 1 (2%)	22 (35%) 7 (11%) 1 (2%)	41 (65%) 17 (27%) 5 (8%)

Source: Author's Laboratory Analysis

Table 2: Bacterial Species Isolated from Participants from each study sites

Bacterial Isolates	**Site Found**	**Bacteremia + UTI**	**Freq.of Bacteria**	**Bacteremia only**	**Freq. of Bacteria**	**UTI only**	**Freq. of Bacteria**
E.coli (Total:22)	All Sites: A, S & I	YES	14	YES	5	YES	3
Kleb.oxytoca (Total:8)	All Sites: A,S & I	YES	5	YES	3	NO	-
K.ozaenae (Total:6)	All Sites: A,S & I	YES	4	YES	1	YES	1
K. Ascorbata (Total:4)	2 Sites: A&I	YES	4	NO	-	NO	-

K.pneumoniae (Total:2)	2 Sites: S&I	NO	-	YES	2	NO	-
Acinetobacter haemolyticus (Total:3)	2 Sites: A & I	YES	2	YES	1	NO	-
A. Baumanii (Total:5)	All Sites: A, S & I	YES	4	YES	1	NO	-
Citrobacter freundii (Total:4)	2 Sites: A&I	YES	3	YES	1	NO	-
C.gillenii (Total:4)	All Sites: A,S &I	YES	1	YES	2	YES	1
Enterobacter Agglomerans (Total:3)	2 Sites: S & I	YES	2	YES	1	NO	-
Stenotrophoma maltophilia (Total: 1)	1 Site: Alimosho	YES	1	NO	-	NO	-
Averyella dalhousiensis (Total:1)	1 Site: Ikorodu	YES	-	YES	1	NO	-

Abbreviation: Sites: Alimosho(A), Surulere (S), Ikorodu (I)
Source: Author's Laboratory Analysis

The total number of samples tested were 660 venous blood and the mid-stream urine samples of participants from Alimosho, Surulere, and Ikorodu LGA in Lagos. Equal numbers of participants (220) in each site were enrolled with consent of their care givers. Baseline characteristics of the participants are listed in table 1. Total number of male participants were 271(41%), bacterial pathogens were isolated from 30 (48%) of them, while 389 (59%) female participants were enrolled for the study and 33 (52%) of them were found with bacterial pathogens.
The oldest participants were from Surulere with a mean age of 3.9 while the youngest were from Ikorodu with a mean age of 3.2. The majority of participants from the 3 sites used borehole as their primary source of drinking water (77%) while a reasonable number of participants (35%) from Ikorodu still used other sources of drinking water. Generally, their caregiver had a good knowledge of febrille illness (433 of 660: 66%). Alimosho had the highest knowledge of febrile illness (70%) while Ikorodu had the least (62%). Low haemoglobin level was observed in the majority of the participants (66%) and in 79% of participants with bacterial pathogens. The number

of infected subjects with bacteremia plus UTIs were 63% , only bacteremia (29%), and only UTIs (8%).
In table 2, The Microbact test kit identified 63 bacterial pathogens of which the most frequent pathogen identified in all the sites were *E.coli* and *Klebsiella spp*. A rare pathogen , *Averyella dalhousiensis* was found only in Ikorodu site. The bacterial isolates were characterized into bacteremia with UTI (63%),only bacteremia (29%), and only UTI (8%).The significant association was between bacteremia with UTI in which most of the pathogens were found.

Discussion of Findings
This study provided an update on the recent spectrum of Gram negative bacterial isolates causing febrile illness in children. Upon, analysing 660 venous blood and urine samples of under- 5 aged children with febrile illness, 9.6% (63 of 660) were found to be infected. The symptoms shown (Table 1) by the participants were typical of febrile children across the globe (Rakotozandrindrainy et al, 2021, Hercik et al, 2018). Despite the knowledge of their caregivers on febrile illness (66%) and good source of drinking water (Borehole:79%) bacterial pathogens were still found in the little children enrolled for this study.Generally, Lagos residents rely on ground water as their major source of drinking water, but a reasonable number (35%) from Ikorodu still depended on other sources of natural water which surrounds the locality.There is significant lack of well maintained public water facilities in Lagos, where urban development processes frequently takes place.This leads to contamination of water bodies with domestic waste including shallow ground water that is less than 70m deep (Obiora & Onwuka, 2005 , Aigheyesi & Edore, 2019).

The caregivers from all the location had good knowledge of Febrile illness. Majority of the participants had low hemoglobin values (Hb < 10g/dl: 66%). The impact was more on those infected with bacterial pathogens (79%). This may be attributed to poor nutrition due to economic constraint in the country as a whole (Aigheyisi & Edore, 2019).The number of infected females were 52% (33 of 63) and males 48% (30 of 63). This is contrary to other publications which reported that males are mostly infected with UTI in their early years (Tullus & Shaikh, 2020). This may be attributed to the higher number of female participants attending the healthcare facilities and consequently being enrolled for the study.

Leucocytouria was seen in 71% of urine samples and nitrite was seen in 59% of samples. It has been shown that at least 10% of children with a UTI do not have white blood cells or leucocyte esterase present in their urine which is especially true in UTI cases caused by organisms other than *E.coli* (Stocker et al, 2021). The sensitivity and specificity of leucocyturia are low because most children with fever and non urinary tract infection may also have leucocyturia (Stein et al, 2015) on the other hand a nitrite detection in urine and bacteriuria has a very high specificity and is commonly used to diagnose UTIs. However, the sensitivity of nitrite in urine is only 50% (Stocker et al, 2021). This is attributed to the fact that not all bacteria produce nitrite and the process of production is time-consuming. Nitrite detection test should be used in combination with other relevant tests. A finding of ≥ 5wbc/hpf in the spun urine or any bacteria is presumptive evidence of a urinary tract infection. Absence of pyuria does not rule out UTI, but only a culture test is diagnostic (Stocker et al, 2021).

A further difficulty is that in young children with presumptive UTIs, around 20% of cultures show lower bacterial numbers than the generally used cutoff of 10^5CFU/mL (Tullus & Shaikh, 2020, Ombelet et al, 2019). In Table 2, the most prevalent pathogen found in all the study sites was *E.coli*

(35%). This finding corresponds to other studies (Mostafa et al, 2022, Tullus & Shaikh, 2020 and Stocker et al, 2021), although in the first year of life *Klebsiella pneumoniae, Enterobacter spp*, *Enterococcus spp*, and *Pseudomonas spp* are more frequent than later in life, and there is a higher risk of urosepsis compared with adulthood (Stocker et al, 2021). Bacterial pathogens isolated were associated with bacteremia plus UTI, bacteremia, and UTI. Most of the bacterial isolates (65%) were found to be present in both blood and urine samples. Bacteremia is a recognised risk associated with UTIs (Smith & Nehring, 2023, Marks et al, 2021) and it is not unique to any particular region, its occurrence in Nigerian children is not surprising given the potential for bacterial spread.

The commonest bacteria found in all the study sites were, *E.coli*, *K.oxytoca* , *K.ozaenae*, *A.baumanii* and *C.gillenii*. They are capable of neutralizing antibiotics effects by releasing beta-lactamases to inactivate beta-lactams (Tacconelli,2018).The *Acinetobacter baumannii* which is among the bacterial isolate in this study is among the WHO priority list of multi drug resistant bacteria (Wasfi et al, 2021, Mabrouk et al, 2020, Tacconelli et al, 2018) . A rare bacterial pathogen, Averyella dalhousiensis (Andrew et al, 2017) was isolated from a participant in Ikorodu. This bacterial pathogen is capable of causing sepsis if immunity is low (Olorukooba et al, 2020).

Both bacteremia and low haemoglobin are identified as risk factors of UTIs in this study. Bacteremia can progress to sepsis when immune system overreacts to the infection and attacks normal tissues and organs (Mostafa et al, 2022, Smith & Nehring, 2023). Low haemoglobin level (Hb < 10g/dl) was found in most of the study participants(66%) and in 79% of participants with bacterial pathogens. This results is worrisome considering the age of this children. Proper management and treatment of febrile children with the aim of reducing under-5 mortality rate in Nigeria is recommended. This could be achieved by carrying out a comprehensive medical investigations on febrile little children as a guideline for proper diagnosis to rule out non-malarial causes of febrile illness.

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