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Bacteriological Profile, Antimicrobial Susceptibility Patterns and Predictors of Bacteremia in Neonates with Clinical Sepsis at KCMC Hospital, Northern Tanzania

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Abstract

Background: Despite a significant decline in neonatal deaths in the last 20 years (5 million in 1990 to 2.4 million in 2019), the risk of death is still high, especially in developing countries. In Tanzania, neonatal sepsis is the third leading cause of neonatal death, accounting for 25% of all deaths. The rising global threat of antimicrobial resistance and the rising burden of neonatal death due to neonatal sepsis have been of great concern and have delayed progress toward reaching SDG goal 3.2 by 2030. This study aims to determine the bacteriological profile, antibiotic susceptibility patterns, and predictors of bacteremia among neonates with clinical sepsis at KCMC Hospital in Northern Tanzania. **Methodology**: This study had a cross-sectional design conducted at KCMC Hospital, Northern Tanzania. The study population was neonates admitted to the neonatal unit at KCMC Hospital. Data were collected using questionnaires and blood cultures from neonates. Frequencies and proportions were used to summarize categorical variables, while continuous variables were summarized using mean and standard deviation. The frequencies and proportions of bacteria isolated and the antimicrobial susceptibility results were analyzed and compared using Pearson's chi-square test and Fisher's exact test where applicable. Modified Poisson regression model was used to determine factors associated with positive blood culture. **Results:** Out of 411 neonates with a clinical diagnosis of neonatal sepsis, 175 (42.9%) had positive blood cultures. Gram-positive bacteria were most

frequently isolated at 52.3%, and gram-negative bacteria were 47.7%. Coagulase-negative *Staphylococcus* (30.7%) and *Staphylococcus aureus* (19.9%) were the predominant gram-positive isolates. Gram-negative isolates were *Klebsiella spp* 47 (26.7%), *E. coli* 10 (5.7%), and *Citrobacter spp* 10 (5.1%). The gram-positive isolates were sensitive to vancomycin, piperacillin/tazobactam, and ceftazidime, whereas the gram-negative were sensitive to amikacin, meropenem, and vancomycin. The study did not find statistically significant associations between clinical factors and positive blood cultures in bacteremia. **Conclusion:** Gram-positive bacteria are the dominant pathogens in early-onset and late-onset neonatal sepsis. High levels of resistance to ampicillin and ceftriaxone and moderate resistance to gentamycin were observed in both gram-positive and gram-negative bacteria. Gram-positive organisms exhibit better susceptibility rates to vancomycin and ciprofloxacin, while gram-negative micro-organisms are more sensitive to amikacin and meropenem. An effective initial treatment approach for neonatal sepsis would involve a combination of drugs.

Keywords

Bacteriological Profile, Antimicrobial Susceptibility Patterns, Clinical Sepsis, Neonates

1. Introduction

Neonatal sepsis is a life-threatening systemic infection that affects newborn infants within the first 28 days of life as a result of suspected or confirmed infection [1]. It can be classified into two categories: early-onset sepsis (EOS) occurring within 72 hours of life and late-onset sepsis (LOS) developing from 72 hours to 28 days of life [2]. The diagnosis of neonatal sepsis is challenging due to its nonspecific signs and symptoms [2]. Neonatal sepsis continues to be a leading cause of morbidity and mortality, particularly in middle and lower income countries [3].

Despite notable advancements in reducing neonatal mortality globally, Sub-Saharan Africa continues to have the highest neonatal mortality rate worldwide (27 deaths per 1000 live births) accounting for 43% of all global newborn deaths [3]. Central and Southern Asia follows closely with 23 deaths per 1000 live births, contributing to 36% of global newborn deaths [3]. In 2020, Tanzania ranked tenth among countries with high neonatal mortality rates at 43 per 1000 live births [3]. The most frequent causes of neonatal death are birth asphyxia, neonatal sepsis, premature birth, and birth defects [3]. Neonatal sepsis is the leading cause of infant mortality in Tanzania, responsible for 25% of all deaths [4].

The prevalence of neonatal sepsis varies across different regions and countries. In South America and the Caribbean, the incidence ranges from 3.5 to 8.9 per 1000 live births, while in Asia, it ranges from 7.1 to 38 per 1000 live births [4]. In

Africa, the incidence ranges from 6.5 to 23 per 1000 live births. In Australia and the USA, the incidence is significantly lower, ranging from 1.5 to 3.5 per 1000 live births [4]. In Tanzania, the prevalence was reported as 38% in Mwanza and 25% in Dar es Salaam [5] [6].

Several factors contribute to the predisposition of neonatal sepsis, including prematurity, low birth weight, chorioamnionitis, maternal febrile illness and premature rupture of membranes [7] [8]. Additional factors include proximity to the nearest health facility, frequency of antenatal visits and number of vaginal examinations [9].

Several biomarkers including lactate concentration (Lac), C-reactive protein (CRP), and procalcitonin (PCT) are employed in the prediction of neonatal sepsis [10]. Despite advancements in biomarker use, blood culture continues to uphold its position as the definitive gold standard for diagnosing neonatal sepsis [11].

Neonatal sepsis in developing countries is commonly attributed to pathogens such as *Klebsiella, Staphylococcus aureus*, *Coagulase-negative staphylococcus* and *Escherichia coli* [12]. In contrast, developed countries primarily experience neonatal sepsis caused by Group B *Streptococcus* followed by *E. coli, Staphylococcus aureus, Coagulase-negative staphylococcus, Listeria monocytogenes, Klebsiella spp, Enterococcus species* and *Pseudomonas aeruginosa* [13].

Antimicrobial resistance is prevalent in Tanzania, with rates ranging from 25% to 50% [14]. Notably, there is significant resistance to ampicillin and cloxacillin, moderate resistance to ceftriaxone and cefuroxime, and comparatively lower resistance to amikacin [6]. Unfortunately, the effectiveness of treatment of neonatal sepsis is hindered by the high rate of antimicrobial resistance, which poses challenges in reducing the neonatal mortality rate associated with neonatal sepsis [15].

Globally, there is a growing concern about the threat of antimicrobial resistance (AMR). In response, the World Health Organization has initiated antimicrobial stewardship programs (ASP) to address this issue. These programs include AMR surveillance, which aims to reduce excessive and inappropriate use of antimicrobials [16]. Tanzania implemented a National Action Plan (NAP) on AMR from 2017 to 2022, aligning with the World Health Assembly's resolutions. NAP focuses on optimizing antimicrobial use through appropriate selection, accurate diagnosis, and correct administration for individual patients [15].

Despite the continued endeavors of various stakeholders to address antimicrobial resistance and enhance the treatment of neonatal sepsis, the burden of this condition remains significant. This circumstance poses a challenge in achieving Sustainable Development Goal 3.2, which targets a reduction in the neonatal mortality rate to 12 deaths per 1000 live births [16]. In Tanzania, there is a lack of comprehensive data regarding the bacterial strains responsible for neonatal sepsis and their susceptibility to antibiotics. Moreover, there is no local data to inform about local treatment based on hospital nomograms. This knowledge

gap is crucial in informing clinicians and stakeholders about the extent of the issue concerning antimicrobial resistance and emerging pathogens within the country.

2. Methods

2.1. Study Design and Time

This was hospital based Cross-sectional study design conducted from October 2022 to March 2023.

2.2. Study Population

This study included neonates aged 0 day-28 days of life who were admitted at KCMC neonatal unit from October 2022 to March 2023 with clinical diagnosis of neonatal sepsis.

2.3. Sample Size

The neonates enrolled in the study were 411.

2.4. Sampling Technique

All neonates meeting the inclusion criteria admitted in the neonatal unit at KCMC hospital during the study period from October 2022 to March 2023 were enrolled.

2.5. Variable Definitions

2.5.1 Outcome of Interest

The outcome of interests in this study was the bacteremia, organisms isolated and antimicrobial susceptibility pattern. This operationalized to be a binary variable carrying 1 and 0 for Blood Culture (1-positive (Bacteremia), 0-negative).

2.5.2. Primary Exposure

Background characteristics included Mothers age, marital status, gestation age at delivery (preterm vs term), birth weight, age of the neonate, and sex of the neonate.

Clinical Characteristics included History of Maternal fever, history of PROM, history of chorioamnionitis, history of ANC visits, place of delivery, mode of delivery and history of previous medication.

2.6. Data Collection Tools, Methods and Study Procedures

2.6.1. Data Collection Tools

Data collection questionnaire and laboratory results forms were used as study tools. The questionnaire was used to collect the important information on socio demographic characteristics of study participants, antimicrobial patterns and antimicrobial susceptibility patterns. Also, EHMS numbers were used after identifying the participants.

2.6.2. Data Collection Methods

The mother/guardian of a neonate was informed about the study all procedures

were explained and written consent obtained. All consenting mothers/guardians were interviewed via questionnaire to collect information on social demographic data then EHMS numbers after identifying the participant, followed by physical assessment of the study participant which included taking vitals and performing general examination and systemic examination. Thereafter, venipuncture was done to collect blood samples for blood cultures from each of these neonates.

2.6.3. Study Procedures

The study was conducted at the neonatal unit at KCMC hospital. The principle investigator (me) identified and selected neonates who fulfilled the inclusion criteria. Then fully explained the study protocol to the parent/guardian of the neonates and got written informed consent. Then the principle investigator with the research assistants performed a proper physical examination on eligible neonates and took detailed using a questionnaire prepared in the study. Thereafter blood samples were collected for blood culture. Appropriate treatment was initiated after collection of blood samples and blood culture results.

2.6.4. Sample Collecting Procedure

Hands were washed with soap and water then disinfected with alcohol hand disinfectant. Tourniquet applied and suitable vein was selected. Sterile cloves were doned. The sterile blood culture pack was opened onto the trolley. Povidone iodine poured into the fluid recess located on blood culture tray/pack. Needle and syringe dropped onto sterile field.

The puncture site was cleaned with povidone using aseptic technique. Then 1-2 minutes was allowed for disinfectant to dry. About 2mls of blood sample was collected and inoculated into Brain Heart Infusion Broth as per manufacturer instructions. The tourniquet was released and syringe removed from puncture site and pressure applied. The 2mls of blood was inoculated into a simple Pediatric specific BacT/ALERT blood culture bottle having first disinfected the top of the blood culture bottle with an alcohol swab.

Gently the blood culture bottle was rotated to mix the blood and culture medium. The blood culture bottle was labelled. The laboratory request form completed to include the date and time and patients' number.

Within 1 hour from the time of blood sampling the vials were delivered to the KCRI-clinical microbiology laboratory for incubation using in BD BACTEC™ FX blood culture system.

In the laboratory at 35C aerobically for 7 days. A positive blood culture was indicated by flashing red light. A positive blood culture was aseptically further processed by gram stain, followed by subculture on 5% sheep blood agar, chocolate agar, and MacConkey agar. Broth culture remained in BD BACTEC™ FX blood culture system for 5 days but was examined further after incubation 24 hours.

Identification of the positive culture was performed by conventional physiological and biochemical methods. This included gram stain, catalase reaction, coagulase

reaction, mannitol salt agar, colonies morphology, hemolytic activity on sheep blood agar plates for gram positive bacteria. Media reaction (MacConkey-lactose fermentation) and Triple sugar iron (TSI), Sulphide Indole Motility (SIM), Urease, Citrate, oxidase and colonies morphology in case of gram-negative rods bacteria (CLSI, 2017) (Figure 1).

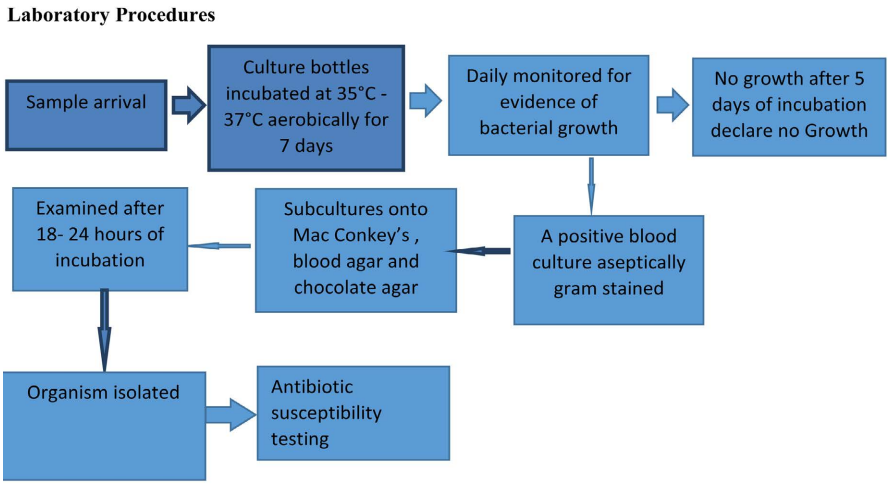

Figure 1. Laboratory procedure of study participant (CLSI, 2017).

2.6.5. Antibiotic Susceptibility Testing (AST)

The antimicrobial susceptibility patterns of all pathogen isolates were determined by the standard disc diffusion method according to Clinical Laboratory Standard Institute. Antibiotic disc was applied to each dried surface of Muller Hilton agar (Becton, Dickinson, USA) after 3 - 5 minutes of inoculation, the antibiotic disc was gently pressed down to ensure complete contact with agar and incubation at 37˚C for 24 hours, zone sizes was measured and interpreted accordingly.

Gram positive bacteria the following were used: penicilin G (10U), clindamycin (2 μg) erythromycin (15 μg), vancomycin (30 μg), ciprofloxacin (5 μg), cefoxitin (30 μg). For Gram negatives: Ampicillin (10 μg), amoxycillin/clavulanate (20/10 μg), gentamycin (10 μg) trimethoprim/sulphamethoxazole (1.24/23.75 μg), ciprofloxacin (5 μg), ceftriaxone (30 μg), ceftazidime (30 μg), amikacin (30 μg) and Meropenem (10 μg), piperacillin/tazobactam (100/10 μg).

All isolates resistance to third generation cephalosporin tested for Extended Spectrum Beta Lactamase (ESBL) production using the disc approximation method. Drug resistance strains in primary screening was further tested for the detection of ESBL in gram negative bacterial isolates and Methicillin resistance Staphylococcus aureus (MRSA) strains in gram positive bacteria. To determine ESBL production, Ceftazidime (30 μg) disc was equidistant from the amoxycillin/clavulanate (20/10 μg) disc; an enhanced zone of inhibition towards amoxycillin/clavulanate (20/10 μg) disc was considered a positive result for ESBL production. A ≥5 mm increase in diameter for antimicrobial agent tested in combination with clavulanate against the zone diameter of the agent when tested alone = ESBL

(CLSI 2022).

Detection of MRSA was done by cefoxitin disc diffusion method placing 30 µg cefoxitin disc on the bacterial lawn culture of *S. aureus.* After overnight incubation, the zone of inhibition was measured. An inhibition zone of diameter less than or equal to 21 mm indicates MRSA.

Interpretation of resistance categories for isolates was done according to the Clinical and Laboratory Standard Institute guideline (CLSI 2022). Organisms which showed resistance to at least one among three or more antimicrobial categories were considered to be multidrug resistance (MDR) bacteria.

2.6.6. Quality Control

E. coli (ATCC 25922) and *Staphylococcus aureus* (ATCC 25923) was used as reference strains for gram negative and gram-positive bacteria, respectively in quality control of culture media, biochemical identification tests and antimicrobial susceptibility testing.

Samples were recorded as negative when no growth was detected within 5 days of incubation following the Clinical and Laboratory Standard Institute guidelines (CLSI) (**Figure 2**).

2.6.7. Data Management and Analysis

Data cleaning and analysis was performed using STATA version 15. Exploration of the data was done in order to check for duplicates, unusual observations and missing values prior to analysis. Missing values on the outcome of interest were dropped from analysis. Some of the variables were re-categorized for proper interpretation between studies. This re-categorization was based on previous literature and plausibility.

Frequencies and proportions were used to summarize categorical variables while continuous variables were summarized using mean and standard deviation. The frequencies and proportions of bacteria isolated and antimicrobial susceptibility results were analyzed and compared using Pearson's chi-square test and Fisher's exact test where applicable.

Classical logistic regression was considered to determine the factors associated with positive blood culture. This approach was not done due the shortcomings of logistic regression of over-estimating odds ratios and 95% confidence intervals for outcomes that were more than 10% prevalence. Since the prevalence of positive blood culture was over 10%, classical logistic regression was not used and therefore, other alternatives to logistic regression were considered.

Log binomial regression was then considered to determine the factors associated with positive blood culture but our analysis failed to converge in multiple log binomial regression. Modified Poisson regression model was used to determine factors associated with positive blood culture.

3. Results

During the study period, between October 2022 and March 2023, a total of 706

neonates were admitted at KCMC to the neonatal Unit. A total of 411 neonates met inclusion criteria, and blood culture specimens from these neonates with clinical diagnosis of neonatal sepsis were obtained within 24 hours of presentation to the neonatal unit.

3.1. Background Characteristics of the Participants

In this study, a total of 411 neonates with a clinical diagnosis of neonatal sepsis were included, among which 175 (42.6%) had positive blood culture results. The majority of participants fell in the age group 0 - 3 days, with early onset neonatal sepsis (EONS)which accounting for 325 (81.9%) and late onset neonatal sepsis (LONS) being seen 86 (18.1%). More than half of the participants (58.6%) were male. A significant proportion of the neonates (50.1%) had a birth weight below 2.5 kg. Regarding delivery, 384 (93.4%) of the neonates were born in hospital. Among these hospital deliveries, the majority were conducted through spontaneous vaginal delivery (SVD). Slightly over half of the neonates were born at a gestational age of 37 weeks or above. Most of the study participants, 385 (93.7%), attended antenatal care (ANC) during their pregnancy. When examining the maternal history, a relatively small percentage of the neonates' mothers had a history of maternal fever (5.6%), chorioamnionitis (4.4%), premature rupture of membranes (23.1%), and previous medication (13.1%) (Table 1).

Table 1. Background and clinical characteristics of study participants and their index mothers admitted to the neonatal ward in KCMC Hospital (N = 411).

Variable	N (%)
Age in days (n = 397)	
0 - 3	325 (81.9)
4 - 28	72 (18.1)
Sex	
Male	241 (58.6)
Female	170 (41.4)
Birth weight in kg	
<2.5	206 (50.1)
2.5 - 4.0	184 (44.8)
>4.0	21 (5.1)
Gestational age during delivery	
<37 weeks	186 (45.3)
37 weeks and above	225 (54.7)

Continued

Mother's education level (n = 378)	
No education	30 (7.9)
Primary education	140 (37.0)
Secondary education	162 (42.9)
College and above	46 (12.2)
History of maternal fever	
Yes	23 (5.6)
No	388 (94.4)
History of chorioamnionitis	
Yes	18 (4.4)
No	393 (95.6)
History of premature rupture of membranes	
Yes	95 (23.1)
No	316 (76.9)
History of previous use of antibiotics during obstetric care	
Yes	54 (13.1)
No	357 (86.9)
Mode of delivery	
SVD	271 (65.9)
C/section	140 (34.1)
Place of delivery	
Hospital/dispensary	384 (93.4)
Home	27 (6.6)
History of antenatal care	
Yes	385 (93.7)
No	26 (6.3)
Blood culture	
Positive	175 (42.6)
Negative	236 (57.4)

SVD—spontaneous vaginal delivery; C/section—caesarean section N total number of study participants.

3.2. The Prevalence of Bacteraemia in Neonates with Clinical Diagnosis of Neonatal Sepsis

The overall prevalence of bacteraemia in the present study was 42.6% (175 of the 411 neonates with clinical diagnosis neonate sepsis) (Figure 2).

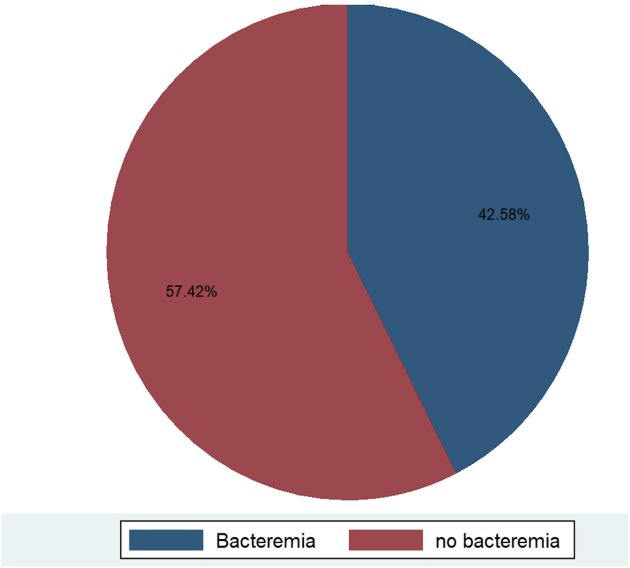

Figure 2. Prevalence of bacteraemia confirmed by positive blood culture among neonates.

3.3. The Bacteriological Profile Obtained from Blood Cultures of Neonates with a Clinical Diagnosis of Sepsis

In this study, the bacteriological profile revealed that gram-positive organisms were the predominant isolates 92 (52.3%), while gram-negative isolates accounted for 84 (47.7%). Among the gram-positive bacteria, *Coagulase-negative staphylococcus* was the most prevalent 54 (30.7%), followed by *Staphylococcus aureus* 35 (19.9%). Among the gram-negative bacteria, *Klebsiella spp.* was the most frequently isolated, 47 (26.7%), followed by *Escherichia coli* 10 (5.7%) and *Citrobacter spp* 9 (5.1%) (Table 2).

Table 2. The bacteriological profile from positive blood cultures of neonates admitted to the neonatal unit at KCMC Hospital in Northern Tanzania (N = 411).

Organism	N (%)	Neonatal sepsis	
		Early onset N (%)	Late onset N (%)
Pseudomonas	2 (1.1)	2 (1.4)	0 (0.0)
Escherichia Coli	10 (5.7)	7 (5.0)	3 (8.3)
Klebsiella spp	47 (26.7)	39 (27.9)	8 (22.2)
Enterobacter spp	3 (1.7)	3 (2.1)	0 (0.0)
Streptococcus virdans	1 (0.6)	0 (0.0)	1 (2.8)

Continued

Streptococcus pneumoniae	1 (0.6)	1 (0.7)	0 (0.0)
Coagulase-negative staphylococcus	54 (30.7)	44 (31.4)	10 (27.8)
Citrobacter spp	9 (5.1)	8 (5.7)	1 (2.8)
Acinetobacter spp	12 (6.8)	10 (7.1)	2 (5.6)
Serratia spp	1 (0.6)	1 (0.7)	0 (0.0)
MRSA	1 (0.6)	1 (0.7)	0 (0.0)
Staphyloccocus aureus	35 (19.9)	24 (17.1)	11 (30.6)

N = number of isolate; MRSA = methicillin resistance staphylococcus aureus; spp = species.

In early-onset neonatal sepsis, the bacteria predominantly isolated were *Coagulase-negative staphylococcus* 44 (31.4%), followed by *Klebsiella spp.* 39 (27.9%), and *Staphylococcus aureus* 24 (17.1%). And in late-onset neonatal sepsis, *Staphylococcus aureus* was identified in 11 (30.6%), followed by *Coagulase-negative staphylococcus* 10 (27.8%), and *Klebsiella spp.* 8 (22.2%) (Table 2). Positive blood cultures were not repeated. However, isolates that were considered contaminants by microbiologists were not included in this study.

3.4. Antimicrobial Susceptibility Patterns of Bacterial Isolates Obtained from Neonates

Assessment of the microbial sensitivity patterns revealed that gram-negative bacteria were susceptible to amikacin, meropenem, and vancomycin. On the other hand, Gram-positive bacteria displayed susceptibility to vancomycin, piperacillin/tazobactam, and ceftazidime.

Of the isolated gram-negative bacteria *Klebsiella* 47 (26.7%) was susceptible to amikacin (100%) and meropenem (86.0%), while *Escherichia Coli* 10 (5.7%) was susceptible to amikacin (100%) followed by meropenem (80%), piperacillin/tazobactam (66.7%) and gentamycin (60%). Additionally, *Citrobacter* 9 (5.1%) the third most isolated Gram-negative bacteria, were highly susceptible to Amikacin (100%), vancomycin (100%) and amoxicillin-clavulanate (100%). MRSA was susceptible to vancomycin (100%) (Table 3).

Table 3. Antimicrobial susceptibility patterns of Gram-positive isolates obtained from neonates with clinical diagnosis of sepsis admitted to the neonatal Unit at KCMC Hospital in Northern Tanzania (N = 411).

Antibiotics	Gram-positive bacteria				
	S. pneumoniae	*S. Virdans*	*CONS* n (%)	*S. aureus* n (%)	MRSA n (%)
AM					
S	-	-	0	1 (25.0)	0
R	-	-	4 (100.0)	3 (75.0)	1 (100.0)

Continued

BP					
S	1 (100.0)	-	0	0	-
R	0	-	34 (100.0)	3 (100.0)	-
GM					
S	-	-	10 (35.7)	10 (31.2)	0
R	-	-	18 (64.3)	22 (68.8)	1 (100.0)
CRO					
S	-	-	0	0	0
R	-	-	2 (100.0)	2 (100.0)	1 (100.0)
CIP					
S	-	-	13 (59.1)	10 (34.4)	0
R	-	-	9 (41.9)	19 (65.6)	1 (100.0)
AK					
S	-	-	0	1 (20.0)	-
R	-	-	4 (100.0)	4 (80.0)	-
MER					
S	-	-	0	2 (100.0)	-
R	-	-	3 (100.0)	0	-
VAC					
S	1 (100.0)	-	44 (95.7)	25 (96.2)	1 (100.0)
R	0	-	2 (4.3)	1 (3;8)	0
PIP/T					
S	-	-	1 (33.3)	1 (100.0)	-
R	-	-	2 (66.7)	0	-
CEZ					
S	1 (100.0)	-	2 (33.3)	1 (100.0)	-
R	0	-	4 (66.7)	0	-
AMC					
S	-	-	0	0	-
R	-	-	3 (100.0)	1 (100.0)	-
SXT					
S	1 (100.0)	0	4 (8.1)	6 (18.2)	1 (100.0)
R	0	1 (100.0)	45 (91.9)	30 (81.8)	0

Continued

CLI					
S	-	-	3 (37.5)	7 (50.0)	0
R	-	-	5 (62.5)	7 (50.0)	1 (100.0)
E					
S	1 (100.0)	1 (100.0)	5 (10.0)	8 (26.7)	0
R	0	0	45 (90.0)	22 (73.3)	1 (100.0)

AM = ampicillin; BP Benzyl penicillin; CRO = ceftriaxone; GM = gentamycin; CIP = ciprofloxacin; AK = amikacin; MER = meropenem; VAC = vancomycin; PIP/T = piperacillin tazobactam; CEZ = ceftazidime; AMC = amoxicillin clavulanate; SXT = sulfamethoxazole/trimethoprim; CLI = clindamycin; E = erythromycin R = resistance; S sensitivity; CONS = *coagulase negative staphylococcus*; MRSA = methicillin resistance staphylococcus aureus.

Of the isolated gram-negative bacteria, *Klebsiella* 47 (26.7) was sensitive to amikacin (100%) and meropenem (86.0%), while *Escherichia Coli* 10 (5.7%) was sensitive to amikacin (100%) followed by meropenem (80%), piperacillin/tazobactam (66.7%) and gentamycin (60%). Additionally, *Citrobacter* 9 (5.1%), the third most isolated gram-negative bacteria, were highly sensitive to amikacin (100%), vancomycin (100%), and amoxicillin clavulanate (100%). MRSA was sensitive to vancomycin (100%). Ampicillin and benzyl-penicillin were highly resistant to Gram-negative organisms (Table 4).

Table 4. Antimicrobial susceptibility patterns of gram-negative bacterial isolates obtained from neonates with a clinical diagnosis of sepsis admitted to the neonatal Unit at KCMC Hospital in Northern Tanzania (N = 411).

Antibiotics	Gram-negative bacteria						
	Pseudomonas	*E. Coli*	*Klebsiella*	*Enterobacter*	*Citrobacter*	*Acinetobacter*	*Seratia*
AM							
S	0	2 (20.0)	0	1 (100.0)	1 (20.0)	1 (10.0)	0
R	2 (100.0)	8 (80.0)	33 (100.0)	0	4 (80.0)	9 (90.0)	1 (100.0)
BP							
S	-	0	0	1 (50.0)	1 (100.0)	0	-
R	-	3 (100.0)	5 (100.0)	1 (50.0)	0	3 (100.0)	-
GM							
S	2 (100.0)	6 (60.0)	25 (55.6)	0	0	5 (45.4)	0
R	0	4 (40.0)	20 (44.4)	1 (100.0)	5 (100.0)	6 (54.6)	1 (100.0)
CRO							
S	-	4 (40.0)	5 (13.9)	0	1 (14.3)	5 (41.7)	0
R	-	6 (60.0)	31 (86.1)	1 (100.0)	6 (85.7)	7 (58.3)	1 (100.0)

Continued

CIP							
S	-	6 (60.0)	13 (31.0)	1 (100.0)	4 (50.0)	3 (33.3)	0
R	-	4 (40.0)	29 (69.0)	0	4 (50.0)	6 (66.7)	1 (100.0)
AK							
S	2 (100.0)	7 (100.0)	14 (93.3)	1 (50.0)	9 (100.0)	3 (42.9)	1 (100.0)
R	0	0	1 (6.7)	1 (50.0)	0	4 (57.1)	0
MER							
S	2 (100.0)	8 (80.0)	37 (86.0)	2 (100.0)	7 (77.8)	3 (37.5)	1 (100.0)
R	0	2 (20.0)	6 (14.0)	0	2 (22.2)	5 (62.5)	0
VAC							
S	1 (50.0)	3 (60.0)	3 (60.0)	2 (100.0)	1 (100.0)	0	1 (100.0)
R	1 (50.0)	2 (40.0)	2 (40.0)	0	0	5 (100.0)	0
PIP/T							
S	2 (100.0)	4 (66.7)	5 (35.7)	1 (100.0)	1 (25.0)	1 (14.3)	1 (100.0)
R	0	2 (33.3)	9 (64.3)	0	3 (75.0)	6 (85.7)	0
CEZ							
S	-	3 (50.0)	3 (9.7)	-	1 (50.0)	1 (20.0)	1 (100.0)
R	-	3 (50.0)	28 (91.3)	-	1 (50.0)	4 (80.0)	0
AMC							
S	0	3 (30.0)	15 (36.6)	-	1 (100.0)	1 (20.0)	0
R	1 (100.0)	7 (70.0)	26 (63.4)	-	0	4 (80.0)	1 (100.0)
FLO							
S	-	-	-	-	-	0	-
R	-	-	-	-	-	1 (100.0)	-
CTX							
S	0	3 (30.0)	2 (4.4)	-	1 (50.0)	2 (25.0)	0
R	1 (100.0)	7 (70.0)	43 (95.6)	-	1 (50.0)	6 (75.0)	1 (100.0)
CLI							
S	-	1 (50.0)	0	-	-	0	0
R	-	1 (50.0)	2 (100.0)	-	-	3 (100.0)	1 (100.0)

Continued

E							
S	-	1 (50.0)	0	-	-	0	0
R	-	1 (50.0)	3 (100.0)	-	-	3 (100.0)	1 (100.0)

AM = ampicillin; BP Benzyl penicillin; CRO = ceftriaxone; GM = gentamycin; CIP = ciprofloxacin; AK = amikacin; MER = meropenem; VAC = vancomycin; PIP/T = piperacillin tazobactam; CEZ = ceftazidime; AMC = amoxicillin clavulanate; SXT = sulfamethoxazole/trimethoprim; CLI = clindamycin; FLO = floxacillin; E = erythromycin R = resistance; S = sensitivity.

3.5. The Predictors of Bacteraemia in Positive Blood Culture Results Among Neonates with a Clinical Diagnosis of Sepsis

In this study, age, place of delivery, mode of delivery, sex, history of chorioamnionitis, and history of premature rupture of membranes were associated with positive blood cultures, but they were not statistically significant. After adjusting for other factors, children with birth weight 2.5 - 4.0 kg had 22% higher prevalence of positive blood culture compared to children with birth weight <2.5 kgs (PR: 1.22, CI: 0.75 - 1.99) and >4.0 kg had 19% higher prevalence of positive blood culture compared to children with birth weight <2.5 kgs (PR: 1.30, CI:0.59-2.82) (Table 5).

Table 5. Factors that predict bacteraemia in positive blood culture results among neonates with a clinical diagnosis of sepsis admitted in the neonatal Unit at KCMC hospital in Northern Tanzania (N = 411).

	Positive blood culture	
Variable	**CPR (95% CI)**	**APR (95% CI)**
Age in days (n = 411)		
0 - 3	1	1
4 - 28	0.96 (0.64 - 1.43)*	0.92 (0.61 - 1.39)*
Sex		
Male	1	1
Female	0.86 (0.64 - 1.15)*	0.89 (0.65 - 1.21)*
Birth weight in kg		
<2.5	1	1
2.5 - 4.0	1.19 (0.88 - 1.61)*	1.22 (0.75 - 1.99)*
>4.0	1.23 (0.64 - 2.37)*	1.30 (0.59 - 2.82)*
Gestational age during delivery		
<37 weeks	1	1
37 weeks and above	1.13 (0.84 - 1.52)*	0.99 (0.61 - 1.63)*

Continued

History of maternal fever		
No	1	1
Yes	1.02 (0.54 - 1.94)*	0.97 (0.48 - 1.98)*
History of chorioamnionitis		
No	1	1
Yes	1.18 (0.61 - 2.32)*	1.30 (0.58 - 2.91)*
History of premature rupture of membranes		
No	1	1
Yes	1.05 (0.74 - 1.49)*	1.07 (0.72 - 1.58)*
History of previous medication		
No	1	1
Yes	1.00 (0.65 - 1.55)*	0.98 (0.59 - 1.61)*
Mode of delivery		
SVD	1	1
C/section	1.06 (0.78 - 1.45)*	1.05 (0.75 - 1.47)*
Place of delivery		
Home	1	1
Hospital/dispensary	1.16 (0.61 - 2.19)*	1.09 (0.57 - 2.11)*
History of antenatal care		
No	1	-
Yes	0.84 (0.48 - 1.48)*	-

*$p \geq 0.05$; **Significant at $p < 0.05$; CPR = Crude Prevalence Ratio; APR = Adjusted Prevalence Ratio; CI = Confidence Interval; SVD = spontaneous Vaginal delivery.

4. Discussion

The aim was to determine the bacteriological profile and antimicrobial susceptibility patterns and predictors of bacteraemia among neonates with clinical diagnosis of neonatal sepsis admitted at KCMC Hospital, Northern Tanzania. The overall prevalence of bacteraemia was 175 (42.6%). Gram-positive organisms were the predominant isolates, accounting for 92 (52.3%), while gram-negative isolates constituted 84 (47.7%). Amikacin and meropenem were highly susceptible to Gram-negative bacteria while vancomycin and ciprofloxacin were highly susceptible to Gram-positive bacteria.

This study demonstrated that the prevalence of bacteraemia was 42.6%. This high bacteraemia was consistent with a study from India, which reported the prevalence of bacteraemia at 54.7% [17] and another study conducted in Nepal that reported the prevalence of bacteraemia at 44.9% [18]. In Tanzania, Mwananyamala Hospital, a higher prevalence of bacteraemia was observed at 72% [19]. In contrast, lower prevalences of bacteraemia have been reported in Kenya 28.6% [20], Uganda 12.8% [21]. In Tanzania at Muhimbili Hospital 19.2% [22]. These differences may be attributed to various factors such as geographical location, differences in culture methods used and the amount of blood volume collected. The high prevalence of bacteremia observed in our study compared to studies from similar settings underscore the need to develop preventive strategies and prioritize the improvement of treatment approaches to combat this condition effectively hence reduce the burden of neonatal mortality.

In this study, a higher proportion of positive blood cultures was seen in cases of EONS than cases of LONS (81.6% vs 8.1%) these proportions align with similar studies conducted in Ethiopia and Uganda, where EONS was reported to be 53.2% [23] and 67.4%, respectively [21]. However, these findings differ from a study conducted at Bugando Hospital in Tanzania, which reported that the majority of neonatal sepsis cases were attributed to LONS at 60%, while EONS accounted for 40%. The lower proportion of bacterial isolates in EONS cases might be due to the use of antibiotics during obstetric care. The use of antibiotics for obstetric care might influence the blood culture results of the newborns as there is a substantial transplacental transfer of antibiotics to the fetus [24]. Early-onset sepsis is associated with high mortality among neonates worldwide [25]. Therefore, it is crucial to strengthen the diagnosis and treatment for early-onset sepsis to prevent neonatal deaths.

The bacteriological profile in this study showed most isolates were Gram-positive mostly *coagulase-negative staphylococcus* and *S. aureus* (**Table 3** and **Table 4**). This resembles that seen in a study in Tanzania [19], in India [26] and in Ghana [27]. In Bugando Hospital Tanzania also found Gram-negative isolates to be more prevalent [5]. This difference could have stemmed from various factors related to the region's microbial ecology, healthcare practices, and antibiotic usage. The organisms in the profile seen in this study are consistent with nosocomial transmission, as shown by a study from India [28]. It is therefore plausible that our neonates acquired the infections through nosocomial infections from being handled by healthcare workers. A study of healthcare worker carriage might be able to shed more evidence on this.

In this study amikacin and meropenem exhibited high susceptibility to gram-negative bacteria, while vancomycin and ciprofloxacin showed high susceptibility to Gram-positive bacteria and high resistance to ampicillin and moderate resistance to gentamycin. Similarly to other studies done in Tanzania in Muhimbili hospital, high resistance was found ampicillin and gentamycin. These are first line therapy [22] and in Mwanyamala hospital, a similar pattern of resistance was

observed [19]. These findings differ slightly from a study conducted in India, which reported different susceptibility patterns for gram-negative and gram-positive bacteria in which Imipenem and Amikacin were reported as highly susceptible to gram-negative bacteria, while Linezolid and tetracycline were highly susceptible to Gram-positive bacteria [26]. Similarly, a study conducted in Odisha (India) reported different antibiotic susceptibility patterns with collistin and aminoglycosides being highly susceptible to Gram-negative bacteria, and vancomycin and Linezolid being highly susceptible to gram-positive bacteria [29]. The differences in antibiotic susceptibility patterns observed across these studies may be attributed to variations in the use of specific antibiotics for testing susceptibility and differences in local prescribing practices. The antibiotic sensitivity test conducted in our study provides relevance in guiding treatment decisions based on local susceptibility patterns. The valuable insights for selecting appropriate drugs helps to reduce the neonatal mortality associated with sepsis.

In this study the association between various factors and positive blood cultures in neonatal sepsis were investigated Factors such as age, place of delivery, mode of delivery, sex, history of chorioamnionitis and history of premature rupture of membranes were examined. However, these factors did not show statistically significant association with positive blood cultures though these factors were clinically significant. This finding differs from a study conducted in Mwanza, Tanzania which reported significant association between positive blood cultures and factors such as inability to feed, lethargy, cyanosis, meconium-stained liquor, premature rupture of the membranes, and convulsions [5]. A study in Dodoma, Tanzania showed maternal factors that predicted early onset neonatal sepsis included maternal history of chorioamnionitis, HIV status, PROM, and multiple digital vaginal examinations during labor and neonatal factors included perinatal asphyxia and being HIV-exposed [30]. Similarly, a study conducted in Meter Hospital, Nairobi, identified significant associations between positive blood cultures and factors such as place of birth, maternal level of education, maternal vaginal discharge, birth weight less than 2500 grams, and the presence of severe abdominal distension [31]. The variations observed across these studies may be attributed to differences in study populations, sample sizes and diagnostic criteria. While our study did not find statistically significant associations between these factors and positive blood cultures, it is important to note that the presence or absence of statistical significance does not necessarily imply the absence or presence of a true association. Further research is needed to better understand the relationship between these factors and positive blood cultures in neonatal sepsis.

Neonatal sepsis poses a grave risk to life and demands urgent treatment with antibiotics. Understanding the causative agents of neonatal sepsis and their susceptibility to antibiotics is crucial for effective intervention. It is vital to emphasize that initiating empirical antibiotic therapy is paramount while awaiting the results of blood culture. Consequently, the initial empirical antibiotic regimen should

consist of a combination of drugs to provide broad coverage against the predominant bacterial organisms in the specific geographic region.

5. Study Limitation

The high usage of antimicrobials before conducting blood cultures may impede the identification of organisms that are susceptible to commonly prescribed antimicrobials. Since many neonates are referred to KCMC from other healthcare facilities and are often treated with antimicrobials prior to referral, this could lead to an underestimation of the prevalence of bacteremia.

The study's findings may be limited to the specific region of Northern Tanzania and may not be generalizable to other locations. The study did not find statistically significant associations between certain clinical factors and positive blood cultures, suggesting a need for further research with larger sample sizes.

6. Strengths of the Study

The study provides valuable insights into the bacteriological profile and antimicrobial susceptibility patterns of neonatal sepsis in the Northern Tanzania. The study demonstrates a relatively large sample size, which enhances the reliability and generalizability of the findings within the studied population.

7. Conclusion

Gram-positive bacteria isolates are the predominant pathogens in both early-onset neonatal sepsis and late-onset neonatal sepsis. Both gram-positive and gram-negative bacteria showed high resistance to commonly prescribed antibiotics ampicillin and gentamycin. Based on the findings from this study gram positive organisms are sensitive to vancomycin, ceftazidime and piperacillin tazobactam and gram negative are susceptible to amikacin, vancomycin and meropenem. An effective initial treatment approach for neonatal sepsis would involve a combination of drugs.

Ethical Considerations

The study was approved by Kilimanjaro Christian Medical University College Research and Ethics Committee before the commencement of the study. The parent study obtained ethical approval from ICF Institutional Review Board (IRB) as well as from the local IRB in Tanzania and informed consent was obtained from all the study participants. All the issues related to confidentiality adhered.

Availability of Data and Materials

Data are available upon reasonable request. All data generated or analysed during this study are available from the Kilimanjaro Christian Medical University College upon reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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