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CAUSATIVE ORGANISMS, ANTIBIOTIC SENSITIVITY PATTERNS AND RISK FACTORS ASSOCIATED WITH NEONATAL SEPSIS AT MOI TEACHING AND REFERRAL HOSPITAL, KENYA
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CAUSATIVE ORGANISMS, ANTIBIOTIC SENSITIVITY PATTERNS AND RISK FACTORS ASSOCIATED WITH NEONATAL SEPSIS AT MOI TEACHING AND REFERRAL HOSPITAL, KENYA

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ABSTRACT

***Background*: Neonatal bacterial infections have been associated with rising antimicrobial resistance levels. This has led to increasing neonatal morbidity and mortality in poorly resourced health facilities located in low-income countries. Local studies on neonatal antibiotic sensitivity patterns and its associated risk factors could inform empirical antibiotic therapy and hospital infection control strategies.**

***Purpose*: This study aimed at determining the causative organisms, antibiotic sensitivity patterns and risk factors associated with neonatal sepsis at a tertiary teaching hospital in Western Kenya.**

Materials and Methods: Cross-sectional study among neonates suspected to have sepsis and undergoing treatment at Moi Teaching and Referral Hospital (MTRH's) newborn unit (NBU) between September 2017 and July 2018. Blood culture tests isolated bacteria and determined their antimicrobial sensitivity. Neonatal and maternal characteristics were obtained through medical chart reviews. Descriptive statistics, Pearson chi-square test of association and odds ratios were adopted.

***Results*: The study enrolled 141 neonates, majority (57.4%) of whom were female. The median gestational age and birth weight were 37 (IQR: 22-45) weeks and 2400g (IQR: 800 - 4700) respectively. Of the 151 bacterial isolates identified, 46.4% were *Klebsiella spp.* followed by *coagulase-negative Staphylococci* (CoNS) at 27.8%. *Klebsiella spp.* was sensitive to meropenem, amikacin and cefepime but resistant to ceftriaxone, gentamicin and cefotaxime. However, CoNS was sensitive**

to vancomycin and penicillin. Both the neonatal and maternal risk factors assessed were not associated with neonatal sepsis.
***Conclusion*: The main bacterial causes of neonatal sepsis were *Klebsiella spp*. and CoNS which were both sensitive to meropenem and amikacin.**

INTRODUCTION

Neonatal sepsis is a clinical syndrome - in an infant up to 28 days of age - which manifests by systemic signs of infection [1]. It is a major cause of neonatal morbidity and mortality globally that can be can be confirmed by isolating the causative pathogen(s) from the blood stream [2]. Approximately 2 million of the 30 million neonates who contract infections annually around the globe succumb to neonatal sepsis [3]. Although the neonatal mortality rate in the developed economies stand at 0.69 deaths per 1000 live births; higher rates of 0.76 deaths per 1000 live births have been reported in the low and middle income countries [3]. The global incidence rate of neonatal sepsis is at 22 per 1000 live births with an estimated mortality rate of 11%-19% [4]. The mortality rate due to neonatal sepsis in Africa has been estimated at 12% in Nigeria [5] and 28% in Kenya [6].

Neonatal sepsis is commonly caused by bacteria that can be classified based on gram staining patterns as either gram-positive or gram-negative. In countries with developing economies, gram-positive organisms such as coagulase-negative *Staphylococci* (CoNS), *Enterococcus faecalis*, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* (MRSA/MSSA) and *Streptococcus pneumoniae* are the most predominant causative organism [7]. On the other hand, gram-negative bacteria such as *Klebsiella pneumoniae, Serratia marcescens, Acinetobacter baumannii* and *Escherichia coli* have been associated with neonatal sepsis in high-income countries [8]. Neonatal sepsis [3] can further be classified based on the time of onset of symptoms as either early onset (≤72 hours of life) or late onset (>72 hours of life) [2,9–11]. Early onset neonatal sepsis (EONS) is associated with causative factors [12] of maternal origin (vertical transmission); while late onset neonatal sepsis (LONS) could be either community acquired or nosocomial among hospitalized neonates [11,13,14]. In the United Kingdom, early onset neonatal sepsis associated with gram-negative bacteria has been reported to be susceptible to a combination of penicillin and gentamicin (94%), amoxicillin and cefotaxime (100%), amoxicillin and other penicillin (98%) and cefotaxime monotherapy at 96% [15]. However, majority of the gram-positive bacteria resisted these treatment combinations. Frequent use of third generation cephalosporins drive the development of resistance bacterial pathogens in neonatal intensive care units and could lead to an emergence of extended spectrum beta lactamase producing strains. Due to limited data in Western Kenya, the antibiotic sensitivity patterns of these bacteria are not well known.

Most early onset neonatal sepsis cases are associated with both maternal and neonatal factors [16]. The maternal factors include age of the mother, level of education, intrapartum pyrexia, parity, attendance of antenatal clinic and presence of urinary tract infection in pregnancy [2,17]. Neonatal risk factors such as APGAR (appearance, pulse, grimace, activity and respiration) score, mode of

delivery and gestational maturity have also been associated with neonatal sepsis [13,18]. There is need to determine the causative organisms of neonatal sepsis in clinical settings and their sensitivity patterns to inform localized infection control strategies, improve on therapy selection, patient care and clinical outcome. This study therefore aimed at determining the causative organisms, antibiotic sensitivity patterns and risk factors associated with neonatal sepsis.

MATERIALS AND METHODS

This was a cross-sectional descriptive study conducted at the newborn unit (NBU) of Moi Teaching and Referral Hospital (MTRH). The facility which is the second largest referral hospital in Kenya and is in the Western part of the country in Uasin Gishu. The study targeted neonates admitted to NBU with a provisional diagnosis for sepsis between September 2017 to July 2018. Venous blood (1ml) was collected aseptically by trained clinicians and transferred into Beckton and Dickinson (BD) pediatric blood culture bottles. Culture and sensitivity assays were performed using BACTEC blood culture test protocol throughout the entire study. Maternal and neonatal demographic and clinical characteristics data were collected from the existing medical records. The study received ethical approval from the Institutional Research and Ethics committee (IREC) of Moi University and MTRH. A parental informed consent was obtained from all the mothers by a trained research assistant who explained the scope, objectives, methods, risk and benefits associated with the study. The bacterial isolates obtained were classified as either gram-positive or gram-negative. The sensitivity patterns of the various antimicrobials were assessed for the various positive isolates. Descriptive statistical techniques were used to summarize the findings as frequencies, mean and median with corresponding proportions, standard deviations and inter quartile ranges. Inferential statistics techniques such as one sample t-test and bivariate analysis were conducted to determine any significant differences and odds ratios between the predictor and outcome variables.

RESULTS

The study enrolled 141 neonates majority of whom (57.4%) were female. The median gestational age at the time of birth was 37 (IQR: 22-45) weeks. Spontaneous vertex delivery (SVD) was the commonest among mode of delivery for 110 (78%) of the neonates enrolled, who had a median birth weight of 2400 grams (IQR: 800 - 4700) with 47.5% having a normal birth weight (Table 1).

Table 1

Characteristics of the neonates with neonatal sepsis at MTRH NBU

Characteristic	N	Frequency (%) / Median (IQR)
Gender	141	
Male		60 (42.6%)
Female		81 (57.4%)
Gestational Age	125	37 (22 - 45) weeks
Mode of Delivery	141	
SVD		110 (78%)
C/S		31 (22%)
Birth Weight	139	2400 (800 - 4700) grams
ELBW		6 (4.3%)
VLBW		24 (17.3%)
LBW		41 (29.5%)
Normal		66 (47.5%)
Macrosomia		2 (1.4%)
Prematurity	141	
Preterm		98 (69.5%)
Term		43 (30.5%)

The median age of mothers enrolled was 24 (IQR: 15 - 40) years majority (54.1%; n=72) of whom were primigravida. Nearly all (93.1%; n=108) respondents attended antenatal clinic, more than half (56.6%; n=69) were unemployed with the more than one-quarter having attended a tertiary educational institution (Table 2).

Table 2
Characteristics of participants' Mothers

Characteristic	N	Frequency (%) / Median (IQR)
Age	136	24 (15 - 40) years
Parity	133	
Primigravida		72 (54.1%)
Multigravida		61 (45.9%)
2		29 (21.8%)
3		20 (15%)
4		2 (1.5%)
5		4 (3%)
6		3 (2.3%)
7		3 (2.3%)
ANC Attendance	116	
Yes		108 (93.1%)
No		8 (6.9%)
UTI	130	
Yes		19 (14.6%)
No		111 (85.4%)
Employment Status	122	
Employed		53 (43.4%)
Unemployed		69 (56.6%)
Level of Education	132	
Primary		50 (37.9%)
Secondary		45 (34.1%)
Tertiary		37 (28%)

Out of the 151 bacterial isolates identified at the neonatal unit of MTRH, majority (46.4%; n=70) were Klebsiella *spp* followed by *Coagulate negative staphylococcus spp* (27.8%; n=42). *Acinetobacter spp.* (6.6%; n=10), *Staphylococcus aureus* (4.7%; n=7), *Enterococcus fecalis* (3.3%; n=5), *Escherichia coli* (2.6%; n=4) had lower frequencies (Table 3).

Table 3

Frequency of Bacterial Isolates at MTRH Neonatal Unit

BACTERIAL ISOLATE	Gram stain	n	Proportion (%)
Klebsiella spp.	Negative	70	46.4
Coagulate negative staphylococci (CoNS)	Positive	42	27.8
Acinetobacter baumanni.	Negative	10	6.6
Staphylococcus aureus spp	Positive	7	4.7
Enterococcus fecalis	Negative	5	3.3
Enterobactor spp	Negative	4	2.6
Escherichia coli	Negative	4	2.6
*Methicillin susceptible staphylococcus aureus (*MSSA*)*	Positive	3	2
Alcaligenes faecalis.	Negative	1	0.7
Methicillin resistant staphylococcus aureus (MRSA)	Positive	1	0.7
Micrococcus spp.	Negative	1	0.7
Pseudomonas auroginosa	Negative	1	0.7
Streptococcus viridans	Positive	1	0.7
TOTAL		**151**	**100**

Klebsiella spp. (a gram-negative bacteria) was sensitive to meropenem (OR=3.298; 95% CI: 2.219-4.902), amikacin (OR=1.116; 0.920-1.354) and cefepime (OR=1.157; 0.167-8.002). However, there were significantly higher odds of its resistance to vancomycin (OR=2.455; 1.888-3.192, p<0.001) as shown on Table 4.

Table 4

Klebsiella spp Antibiotic Sensitivity and Resistance Patterns

Antibiotic	Pearson chi-square test					
		Klebsiella spp.	**Odds Ratio**	**95% Confidence Interval**		**p-value**
	n(%)			Lower	Upper	
Vancomycin	70 (100)	Resistant	2.455	1.888	3.192	<0.001
Meropenem	57 (81.4)	Sensitive	3.298	2.219	4.902	<0.001
Ceftriaxone	66 (94.3)	Resistant	1.076	0.990	1.061	0.161
Amikacin	54 (77.1)	Sensitive	1.116	0.920	1.354	0.270
Cefepime	68 (97.1)	Sensitive	1.157	0.167	8.002	0.882
Gentamicin	66 (94.3)	Resistant	1.076	0.990	1.061	0.161
Cefotaxime	67 (95.7)	Resistant	1.077	0.983	1.180	0.122

Gram-positive bacteria (CoNS) was sensitive to vancomycin (OR=5.710; 3.478-9.374) and amikacin (OR=1.497; 0.884-2.535), but resistant to the rest. There was a statistically significant association between CoNS and resistance to meropenem (p<0.001) as shown on Table 5.

Table 5

Coagulase Negative Staphylococcus (CoNS) antibiotic sensitivity and resistance

Antibiotic	Pearson chi-square test					
	n(%)	CoNS	Odds Ratio	95% Confidence Interval		p-value
				Lower	Upper	
Cefepime	42 (100)	Resistant	1.038	1.001	1.077	0.208
Cefotaxime	41 (97.6)	Resistant	1.086	1.004	1.175	0.116
Vancomycin	33 (78.6)	Sensitive	5.710	3.478	9.374	<0.001
Penicillin	31 (73.8)	Resistant	0.985	0.937	1.036	0.481
Meropenem	38 (90.5)	Resistant	2.739	2.061	3.642	<0.001
Amikacin	27 (64.3)	Sensitive	1.497	0.884	2.535	0.142
Gentamicin	36 (85.7)	Resistant	1.005	0.868	1.162	0.951
Ceftriaxone	40 (95.2)	Resistant	1.070	0.974	1.176	0.238

Neonatal risk factors such as spontaneous vaginal delivery, hospital delivery, prematurity, Low birth weight and 5-minute APGAR score of ≤6 were not significantly associated with neonatal sepsis (Table 6).

Table 6

Neonatal Risk factors associated with Neonatal Sepsis

Neonatal Characteristics	*Klebsiella sp.*	CoNS
Mode of Delivery (N=141) SVD = 110 (78%) CS = 31 (22%)	p-value = 0.256 RR = 0.868 (0.698 – 1.080)	p-value = 0.557 RR = 1.278 (0.531 – 3.076)
Birthplace (n=134) Hospital = 125 (93.3%) Home = 9 (6.7%)	p-value = 0.144 RR = 1.476 (0.733 – 2.975)	p-value = 0.207 RR = 0.508 (0.194 – 1.332)
Maturity (N=141) Term = 98 (69.5%) Preterm = 43 (30.5%)	p-value = 0.106 RR = 0.826 (0.652 – 1.045)	p-value = 0.792 RR = 1.094 (0.561 – 2.135)
Apgar Score at 5 minutes (N=105) ≤6 = 37 (35.2%) >6 = 68 (64.8%)	p-value = 0.259 RR = 1.532 (0.733 – 3.202)	p-value = 0.352 RR = 0.082 (0.669 – 1.163)

Primiparity, intrapartum pyrexia (IPAP), maternal age, level of education, urinary tract infection (UTI), prolonged rapture of membranes (PROM) and mode of delivery as

the selected maternal risk factors were not associated with the occurrence of neonatal sepsis (Table 7).

Table 7
Maternal Risk Factors Associated with Neonatal Sepsis

Maternal Characteristics	All Infections (p-value)	*Klebsiella sp.*	CoNS
Parity (Primiparity/Multiparity)	0.783	p-value = 0.322 RR – 1.116 (0.895 – 1.391)	p-value = 0.484 RR – 0.787 (0.401 – 1.543)
Intrapartum Pyrexia	0.395	p-value = 0.814	p-value = 0.331
Maternal Age	0.327	p-value = 0.630	p-value = 0.404
Level of Education	0.426	p-value = 0.365	p-value = 0.191
UTI in pregnancy	0.918	p-value = 0.304	p-value = 0.164

DISCUSSION

Neonatal sepsis is caused by various pathogenic bacteria that can be classified as either gram-positive or gram-negative based on their gram staining patterns. In this study, the leading causative organism for neonatal sepsis was *Klebsiella spp* (gram-negative bacteria) which accounted for nearly half of all the bacteria isolated. The second most common bacteria isolated among the neonates enrolled in the study was CoNS (gram-positive bacteria) that accounted for more than one-quarter of all the bacteria isolated. Although there were other bacteria isolated from the neonates enrolled, their proportions were negligible with *Acinetobacter baumannii* (a gram-negative bacteria) being the third most prevalent bacteria isolated.

These results are consistent with those from previous studies conducted in Kenya [19] and India [20]. In a study conducted at Kilifi District Hospital in Kenya, *Klebsiella spp* was the most prevalent of all the bacterial isolates and the leading gram-negative bacteria seen [19]. This similarity could be attributed to the fact that both studies were conducted in public hospitals in the same country where infection control strategies and study participants characteristics are similar.

However, this study's bacterial isolates proportions differ from those reported in previous studies conducted in Kenya [21], Bangladesh [22] and Arab States in the Gulf region – Kuwait, Saudi Arabia and the United Arab Emirates - [23]. In a ten year (2000 - 2009) retrospective review conducted at Aga Khan university hospital – a private teaching hospital in Kenya - CoNS was the most common (27%) bacteria isolated from the neonates followed by *Klebsiella spp* [21]. This difference could be attributed to difference in study settings and design.

In the Bangladesh study conducted at Ad-Din Medical College Hospital (AMCH) in Dhaka; it was reported that CoNS (68.4%) was the most prevalent followed by *Acinetobacter baumannii* at 18.4% [22]; however, there was no *Klebsiella spp* reported. This variation could be attributed to difference in study designs as

the Bangladesh study was prospective over a period of nine-months while the current study was cross-sectional.

In the Gulf Region states [23], it was reported that CoNS was the most prevalent (34.65%) followed by *Klebsiella spp (*22.8%*), E. coli* (4.85%) and *Acinetobacter spp* (4.59%). The prospective study conducted in the NICUs of Kuwait, United Arab Emirates (UAE) and Saudi Arabia was different from the current study due to its study design, target population (late onset sepsis) and sample size (n=780); further explaining the difference in study findings.

Klebsiella spp was sensitive to meropenem (OR=3.298; 95% CI: 2.219-4.902), amikacin (OR=1.116; 0.920-1.354) and cefepime (OR=1.157; 0.167-8.002). However, there were significantly higher odds of its resistance to vancomycin (OR=2.455; 1.888-3.192, p<0.001) and gentamicin (OR=1.907; 1.86-1.95, p=0.163). The sensitivity data in this study were similar to those found in India [20] where *Klebsiella spp* was sensitive to amikacin but resistant to penicillin. These gentamicin sensitivity results are also similar to those reported in the Gulf Region States [24] where *Klebsiella spp* was resistant to gentamicin (8%). In contrast, a study conducted in Kenya reported *Klebsiella spp* to be sensitive to gentamicin (72.4%). Despite this; the findings from Aga Khan hospital demonstrated that *Klebsiella spp* sensitivity to amikacin were similar (94.1%) to those reported in the current study [21].

Coagulase-negative Staphylococci (CoNS) were sensitive to vancomycin (OR=5.710; 3.478-9.374) and penicillin (OR=2.595; 0.166-40.550), but resistant to the rest. These findings compare to a study in India where CoNS was resistant to gentamicin, ceftriaxone and ceftazidime. However, CoNS was sensitive to vancomycin and penicillin. The findings further match those from Bangladesh [22] who found CoNS to be sensitive to vancomycin (74%) while resistant to meropenem (22%) and amikacin (0%). In a previous Kenyan study [21], it was reported that CoNS was sensitive (88.9%) to amikacin and gentamicin (83.4%) which contrast the findings of the current study. This could be attributed to the abuse of gentamycin (a first line antimicrobial) over the years without laboratory diagnostic confirmation.

In this study, there was no statistically significant relationship demonstrated between maternal characteristics and occurrence of neonatal sepsis. Primiparity, intrapartum pyrexia, maternal age, level of education, urinary tract infections, prolonged rapture of membranes and mode of delivery were not significantly associated with neonatal sepsis occurrence. These findings are similar to studies conducted in Saudi Arabia [25], Uganda [26] and South Korea [27]. In the study conducted at King Abdul-Aziz Specialist Hospital in Taif -Saudi Arabia [25], there was no statistically significant association between intrapartum pyrexia and prolonged rapture of membrane. Although both studies adopted a cross-sectional study design, in Saudi Arabia, the neonates were stratified into three groups (proven early-onset neonatal sepsis, clinical early-onset neonatal and negative infectious status) while the current study only had a single group of neonates with sepsis. At Uganda's Mulago hospital [26], the study assessed the aetiology and risk factors for neonatal sepsis and determined that primiparity, intrapartum pyrexia, prolonged rapture of membranes and mode of delivery were not significantly associated with the occurrence of neonatal sepsis. These findings were also similar to those from South Korea [27] where no statistically significant association between prolonged rapture of membranes and

occurrence of neonatal sepsis was reported. In contrast, a study conducted in Ethiopia's public hospitals of Mekelle City [17] reported that the occurrence of neonatal sepsis was significantly associated with intrapartum pyrexia, urinary tract infections and prolonged rapture of membranes.

Furthermore, the selected neonatal risk factors such as spontaneous vaginal delivery, hospital delivery, prematurity, low birthweight and a 5-minute APGAR score of ≤6 were not found to be significantly associated with neonatal sepsis. This was also the case with the findings reported in Saudi Arabia [25], Uganda [26] and South Korea [27].

CONCLUSIONS AND RECOMMENDATIONS

This study determined that the main bacterial causes of neonatal sepsis at a teaching hospital in Kenya were *Klebsiella spp* and CoNS. Both the gram-positive and gram-negative bacteria had good sensitivity to meropenem and amikacin. The risk factors evaluated were not associated with the occurrence of neonatal sepsis. *Klebsiella spp* being one of the known nosocomial infections, improvement in infection control in the unit is recommended. There is need for evidence-based review of empirical antibiotic therapy regimen containing penicillin, gentamycin and ceftriaxone due to the prevailing high resistance levels. Future studies targeting specific risk factors should be conducted.

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