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Antibiotic Resistance and Associated Factors for Neonatal Sepsis at a Selected Children's Hospital in Zambia

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ABSTRACT

Background: Neonatal sepsis is a common condition among neonates particularly in developing countries. Treatment of neonatal sepsis is with antibiotics, which have huge benefits when indications are clear. However, widespread utilisation of antibiotics over the years has been reported to favour the emergence of antibiotic resistance. In this study, we aimed at assessing antibiotic resistance and associated factors for neonatal sepsis at a selected children's hospital in Zambia.
Method: We conducted a retrospective cross-sectional study from January, 2018 to December, 2019. Data was collected from files of all admitted neonates and the microbiology blood culture register. Analysis of factors associated with antibiotic resistance was done by logistic regression using STATA software, version 14 and statistical tests were done using 5% significance level and 95% confidence intervals.
Results: Out of the 172 blood cultures analysed**,** 61.0% (105/172) were male admitted with suspected neonatal sepsis. The median age at admission was 4 (2 - 12) days old and 69.8% (120/172) were positive blood cultures. Commonly isolated bacteria causing neonatal sepsis were *Enterobacter* (29.2%), *E. coli* (19.2%) and *Staphylococcus* (13.3%). Resistance of isolated bacteria towards Penicillins ranged from 80% to 100% and to third generation cephalosporins from 50% to 70% and these were the most commonly resistant antibiotics. An increase in the duration of empirical treatment was more likely (AOR= 1.12, CI: 1.01 - 1.23) to be associated with antibiotic resistance for neonatal sepsis and this finding was statistically significant.
Conclusion: Increased duration of empirical treatment in hospital was a positive predictor for antibiotic resistance. Early detection of bacteria causing sepsis and sensitive antibiotics via blood culture and drug sensitivity testing would probably reduce the rate of antibiotic resistance.

Key words: Antibiotic resistance, neonatal sepsis, Bacteria.

INTRODUCTION

Globally, more than one million neonatal mortalities that may be attributed to severe infections occur annually [(1,2)]. Most of the mortalities resulting from severe infections occur in low-income countries, which harbour several factors that lead to emergency as well as spread of multidrug resistant bacteria [(3,4)]. In Zambia, there is an increase in neonatal mortality rate from an estimated rate of 24 per 1000 live births in 2013 - 2014 to 27 deaths per 1000 births in 2018 and neonatal sepsis is the second cause of death after prematurity [(5)].

Neonatal sepsis (NNS) can be defined as a systemic inflammatory response, manifested by varying vague clinical features brought about by the invasion of microorganisms, their active multiplication in blood and it is confirmed by a positive blood culture test in the first twenty-eight days of life [(6)]. According to

WHO sepsis definition criteria, the microorganisms associated with Early (≤ 3 days) or Late (> 3 days) onset of Neonatal sepsis (EONNS and LONNS) differ both at global and local levels [2,3]. Clinical presentation and symptomatology such as raised temperature, irritability, difficulty in breastfeeding, inactivity and distension of the abdomen as well as signs such as jaundice, increased heart and respiratory rates, pallor, grunting, lethargy, hypothermia, seizures and unconsciousness vary in affected neonates suspected with NNS [7]. The most commonly prescribed drugs in the Neonatal Intensive Care Unit (NICU) are antibiotics, which have an enormous benefit when indications are clear. However, continued as well as widespread utilisation of antibiotics has resulted in a strong selection pressure on microorganisms over the years favouring the emergence of antibiotic resistance [1].

Antibiotic resistance resulting from utilisation and abuse of antibiotics around the world is currently a major health crisis. Neonates are often exposed to antibiotics before and after birth due to empirical administration of antibiotics in order to prevent any risk of an infection or treatment for non-specific signs that may or may not indicate sepsis [8,9]. Many studies have shown resistance to the first and second line antibiotics that are used as empirical treatment in accordance with the National Institute of Clinical Institute (NICE) guidelines [10]. Recommended first line treatment for NNS includes penicillin such as ampicillin or benzyl penicillin and aminoglycoside such as gentamicin. Second line drugs are cephalosporin such as ceftriaxone or cefotaxime [11]. Knowing the most prevalent bacterial isolates and their antibiotic susceptibility pattern is crucial when choosing the appropriate empirical therapy in order to decrease morbidity and mortality [12]. Thus this study investigated the common bacteria for neonatal sepsis, antibiotic resistance and its associated factors for neonatal sepsis at a selected children's hospital in Zambia.

MATERIALS AND METHODS

We conducted a retrospective cross-sectional study at a selected children's hospital known as Arthur Davison Children's Hospital (ADCH) in Ndola, Zambia, from January 2018 to December 2019. ADCH is the largest tertiary and specialised paediatric hospital in the northern region of Zambia. More than 10 neonates are admitted to neonatal intensive care unit (NICU) each day and the majority of the admissions are due to suspected neonatal sepsis.

A total of 172 neonates on whom a blood culture was done were examined during a study period. All admitted neonates with suspected neonatal sepsis and on whom blood culture was done for sensitivity was included in the study. On the other hand, neonates whose culture showed organisms other than bacteria such as fungi were excluded from the study. The microbiology laboratory blood culture register was reviewed for data collection and all file identification numbers for neonates were de-identified. The microbiology laboratory at ADCH follows standard microbiological techniques [13]. The skin is cleaned with disinfectant solution before withdrawal of blood. Thereafter three to five millilitres of blood are drawn aseptically from a peripheral vein and injected into the BACTEC PedsPlus™ (Becton Dickinson, Ireland) culture bottle. Incubation in an automated machine at 37 °C immediately on receipt of specimen is then done for 5 to 7 days. The automated BACTEC machine detects a positive culture within 24 to 72 hours. Then inoculation onto different culture media for Subculture and organism identification is performed. Antibiotic susceptibility test is done using the Kirby-Bauer disc diffusion method [14], as per the Clinical and Laboratory Standards Institute.

Statistical analysis

For descriptive statistics, continuous normally distributed data such as duration of empirical treatment, was summarised using the mean and standard deviation, whereas

median and interquartile range were used for skewed data such as age of neonate at blood culture. Frequency and percentages were used to report categorical data such as birth weight categories. Logistic regression methods were used to determine relationship between the antibiotic resistance and associated factors. All statistical tests were tested at 5% significance level with a 95% confidence level. STATA software, version 14 SE (STATA Corp., College Station, Texas, USA) was used for statistical analysis and for statistical analysis a p-value of less than 0.05 was considered statistically significant.

Ethical considerations

Ethical approval for the study was sought from the University of Zambia Biomedical Research Ethical Committee (Reference number 365-2019) and the National Health Research Authority. Permission to carry out the study and have access to patient information was obtained from Arthur Davison children's hospital management. Confidentiality of patient information was adhered to and names and file numbers of patients were not displayed on the data collecting tool instead serial numbers used in identifying the patients. No files were taken out of the hospital for confidentiality purposes.

RESULTS

Demographic and clinical characteristics of participants

Of the total 172 blood culture results analysed, 69.8% (120/172) were positive blood cultures. Out of the culture positive results, 85.8% (103/120) were Gram negative bacteria and 14.2% (17/120) belonged to the Gram positive cocci. Among the admitted neonates, there were more males accounting for 61.0% (105/172). Admitted neonates had a median age of 4 days with an interquartile range of 2 to 12 days. The temperature of neonates at admission was 37.7°C with a standard deviation of 1.5°C. Neonates who were born with a weight less or equal to 2500 grams were 23 out of 172 (18.0%). This is shown on Table 1.

Table 1: Demographic and clinical characteristics of participants, N=172

Variable	Category	Frequency (%)
Sex		
	Male	105 (61.0)
	Female	67 (39.0)
Place of birth		
	Hospital	35 (48.6)
	Clinic	37 (51.4)
Mode of delivery		
	Vaginary	82 (85.4)
	Caesarian Section	14 (14.6)
Birth weight (grams)		
	≤2500	31 (18.0)
	>2500	141 (82.0)
Child's HIV exposure status at birth		
	Child Not Exposed	75 (85.2)
	Child Exposed	13 (14.8)
Blood culture result		
	Positive	120 (69.8)
	Negative	52 (30.2)
Gram stain		
	Negative bacilli	103 (85.8)
	Positive cocci	17 (14.2)
Temperature (ºC) *	Mean (SD)	37.7 (1.5)
Age at admission (days) **	Median (IQR)	4 (2 - 12)
Age at blood culture (days) **	Median (IQR)	9 (4 - 16)
Duration of empirical treatment (days) **	Median (IQR)	2 (1 - 6)

*NOTE: IQR = interquartile range, SD =standard deviation, * Mean and standard deviation are reported, ** Median and interquartile range reported*

Common isolated Bacteria causing neonatal sepsis

Majority of bacteria isolated were Gram negative bacilli belonging to the

Enterobacteriaceae family with *Enterobacter species (spp)* 29.2% (35/120), being the most common bacteria followed by *E. coli spp* (23/120, 19.2%), *Klebsiella spp* 10.0% (12/120,) and *Serratia spp* 10.0% (12/120,). The most common Gram positive cocci isolated was *Staphylococcus spp* 13.3% (16/120,) as shown in Figure 1.

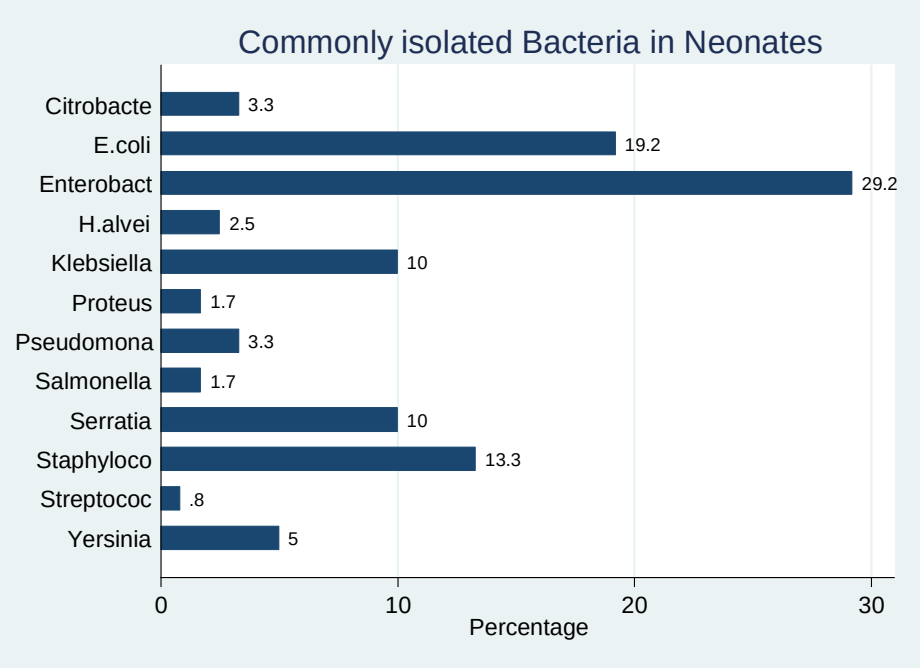
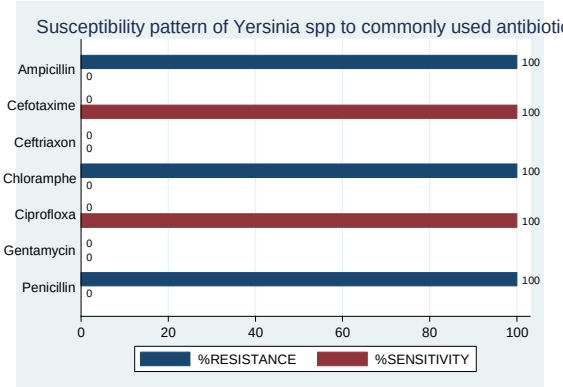


Figure 1: Proportion of commonly isolated bacteria in neonates with neonatal sepsis

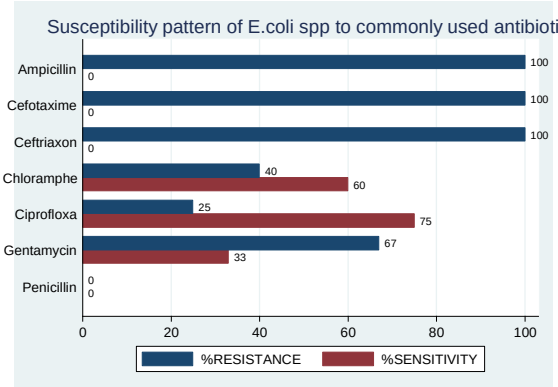
Susceptibility patterns of commonly used antibiotics in the treatment of neonatal sepsis

Figure 2 shows susceptibility patterns of commonly used antibiotics to common isolated bacteria. Most of the antibiotics tested for drug susceptibility were resistant to *Enterobacter spp* (fig. 2 D) followed by *E. coli spp* (fig. 2 B) *and Klebsiella spp* (fig. 2 C). Antibiotics that were tested for susceptibility against *Yersinia spp*, (fig. 2 A) showed either 100% resistance or sensitive, with ampicillin, chloramphenicol and Penicillin-G showing 100% resistance. Ciprofloxacin and chloramphenicol were both at least 60% sensitive. *Staphylococcus spp*, (fig 2 E) which is a Gram positive cocci, showed to develop resistance towards commonly used antibiotics relatively lower compared to Gram negative bacilli that were isolated. Ampicillin was the only drug that showed 100% resistance towards staphylococcus. Resistance to chloramphenicol and cefotaxime were seen to be 100% towards *Serratia spp* (fig 2 F).

A



B



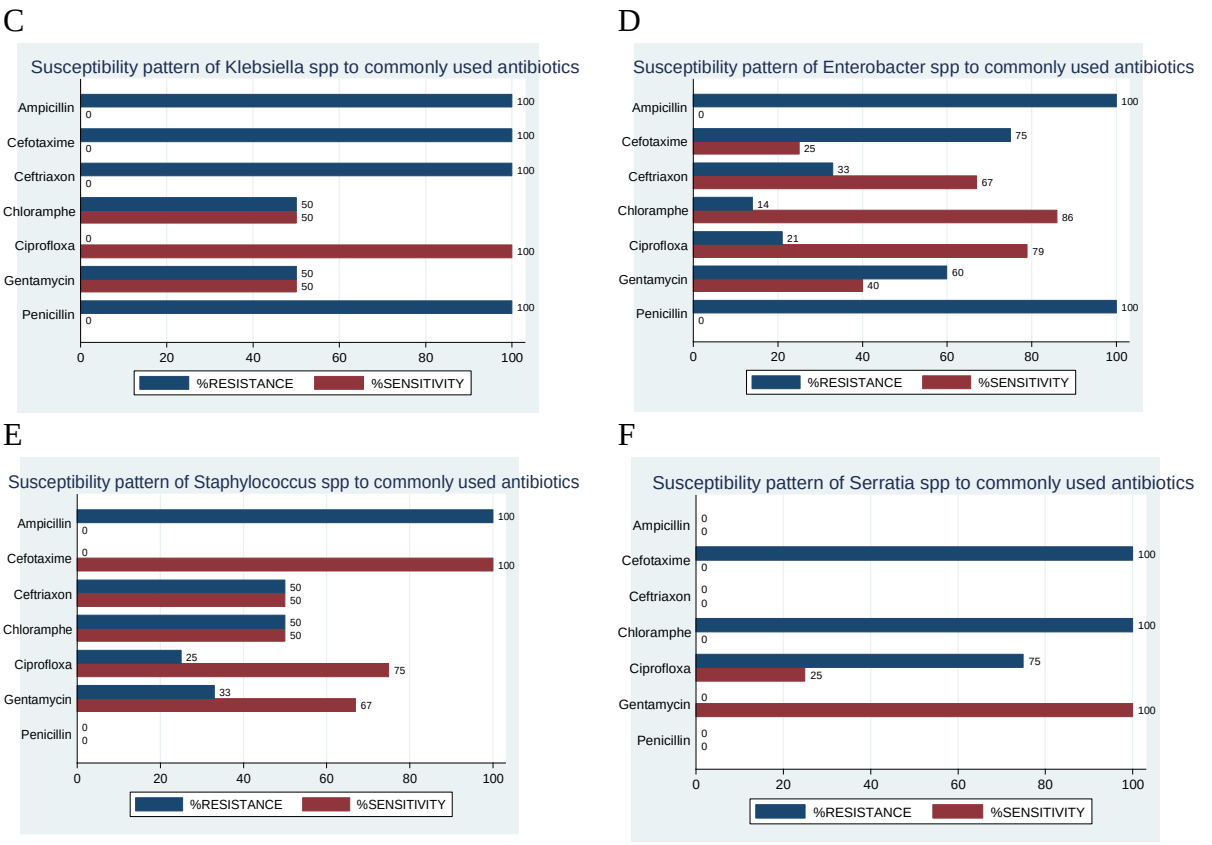


Fig 2: Susceptibility pattern of each commonly isolated bacteria to commonly used antibiotics

Factors associated with antibiotic resistance

Being female had a reduced chance of antibiotic resistance by 65.0% (AOR= 0.35, 95% CI [0.12 – 1.03]; p=0.058) as compared to being male taking into account of the duration of empirical treatment and Gram stain of the bacteria and this finding was not statistically significant. On the other hand, one-day increase in the duration of empirical treatment that a neonate received from time of admission, significantly increased the chance of antibiotics developing resistance to common isolated bacteria by about 12.0% (AOR=1.12, 95% CI [1.01 – 1.23]; p=0.039) after adjusting for the sex of the neonate and Gram stain of the bacteria isolated and this was statistically significant. This is shown in table 2.

Table 2: Unadjusted and adjusted regression analysis for factors associated with antibiotic resistance

Variable	COR	95% CI	P-Value	AOR	95% CI	P-Value
Duration (days)	1.10	1.00 – 1.21	0.053	1.12	1.01 – 1.23	0.039
Sex						
Male	Ref.					
Female	0.67	0.29 – 1.56	0.351	0.35	0.12 – 1.03	0.058
Gram stain						
Negative	Ref.					
Positive	0.26	0.06 1.25	0.093	0.37	0.07 – 1.93	0.236

COR = Crude odds ratio; AOR = adjusted odds ratio; CI = confidence interval

DISCUSSION

This study was set out to assess antibiotic resistance and associated factors for neonatal sepsis at Arthur Davison children's Hospital in Ndola, Zambia. We have found that majority of neonates admitted with suspected neonatal sepsis were male. The prevalence of confirmed sepsis was 69.8%. The common organisms isolated were *Enterobacter species (spp), E. coli spp* and *Staphylococcus spp*. The most resistant antibiotics were penicillins and third generation cephalosporins. Female sex and Gram stain of the isolated bacteria

being positive, were less likely associated with antibiotic resistance while a day increase in the duration of empirical treatment was more likely associated with antibiotic resistance.

Neonatal sepsis is regarded as the leading cause of mortality and morbidity in the NICU. This study found 69.8% prevalence of neonatal sepsis through positive blood culture. The prevalence found in this study is in keeping with finding by Nandini and Vidhya [15] in India which reported 62.8% prevalence for neonatal sepsis. Notably previous studies conducted in neonatal nurseries have shown prevalence of less than 50% for positive blood culture result. For example, 20.7% at Patan hospital in Nepal [16], 33% at University Teaching Hospital in Zambia [11] and 46.8% in India [6]. The variations in blood culture positivity rate of neonatal sepsis in different studies could be due to differences in geographical area and distribution, culture-techniques and blood collection as well as variations in organisms from region to region [16]. The type of study design such as retrospective or prospective as well as whether patients were on prophylactic antibiotics or not before obtaining blood samples for culture could explain the observed higher prevalence in the current study [15,17]. However, the high prevalence in this study could suggest the burden of confirmed neonatal sepsis seen at ADCH despite early administration of antibiotics.

Gram negative bacilli were the majority of the bacteria isolated (85.8%) compared to Gram positive cocci (14.2%). This finding was similar to studies conducted in Nepal and South Asia which reported 60.64%, 77% and 63% (16,18,19). Even though there were similarities in Gram stain, there were differences in the common bacteria isolated. This study found close to one-third *Enterobacter spp* as the most common causative agent of neonatal sepsis, followed by *E. Coli* about one-fifth, and one-tenth of *Klebsiella spp* and *Serratia spp* . In contrast, *Klebsiella spp* was the most common bacteria isolated in Nepal [16,18] and in South Asia [19]. However, other studies conducted in India and Nigeria showed Gram positive cocci to be the most common isolated microorganisms with *Staphylococcus spp* as the most common bacteria causing neonatal sepsis [6,20] which was different from this study. The predominant Gram positive bacteria isolated was *staphylococcus spp* similar to a study conducted in South Asia [19]. Differences in findings could be attributed to variations in adherence to infection prevention practices and control measures, study setting and population as well as hand hygiene practices which has been reported by other researchers to attenuate bacteria species [4,20]. In the current study, differences in findings could be due to timing (immediately at admission or after some post admission) and site of blood collection for culture and sensitivity [21].

Antibiotics belonging to the Penicillin group such as Ampicillin, Penicillin G, Oxacillin were noted to be 100% resistant to most common bacteria isolated in this study. This finding is in keeping with studies done in Tanzania, Nigeria and Zambia [7,11,22,23]. Other commonly used antibiotics that showed resistance were Gentamicin (33% to 67%) and third generation cephalosporins such as cefotaxime (67% to 100%) and ceftriaxone (33% to 100%). This resistance pattern observed could be attributed to prolonged duration of empirical treatment with use of Penicillin-G/ Ampicillin with Gentamicin or third generation cephalosporins [24]. This prolonged duration of antibiotic use could have led to bacteria copying strategy of action thus causing antibiotics to be inactive [22]. However, most of the isolated bacteria were sensitive to ciprofloxacin and chloramphenicol, similar to studies done by Ogundare et al., [22] and Kabwe et al., [11]. These studies did not show the sensitivity of chloramphenicol. Ogundare et al., [22] showed that cefotaxime and ceftriaxone were sensitive which was different from this study.

Although not statistically significant, being female had a reduced chance of antibiotic resistance. This finding could be attributed to the high susceptibility of male neonates towards septicaemia compared to female neonates [6] due to the presence of defective factors regulating the synthesis of gamma globulin being situated probably on the X chromosome in male neonates hence resulting in less immunological protection as compared to female neonates [25]. On the other hand, cell mediated immune response has been observed to be suppressed by male sex hormones such as androgens thus conferring a natural disadvantage in septic conditions [26]. Despite neonates being on empirical treatment on admission, there was a high prevalence of positive blood culture results (69.8%) which could be attributed probably to most drugs having developed resistance to commonly isolated bacteria causing neonatal sepsis. A day increase in the duration of empirical treatment increased the chance of antibiotic resistance. This could be due to the fact that most isolated bacteria in this study were Gram negative and produce the extended spectrum beta lactamase enzyme that cause most antibiotics to be resistance especially with increased duration of treatment with no known causative agent [9]. On the other hand, empirical treatment administered to neonates prior or upon admission could have been inappropriate antibiotics and doses [27]. A study by Micek *et al*, [28] noted that an increased duration of stay for patients in hospitals, increased the likelihood of patient colonization and subsequent infection with antibiotic-resistant bacteria. This was in keeping with the finding in this study.

This study had limitations worth noting. First, the study was based on secondary data, thus there was no much control over the data that were found in the files. Variables having greater than 5% missingness were omitted in the full model analysis to prevent convergence errors. The results of this study cannot be generalized as this study was done at one hospital. There is also a possibility of changes in the resistance patterns as well as isolated bacteria as this was retrospective. However, the findings in this study reflect the situation at the institution as limitations such as degree of missingness, were taken into consideration at all costs.

CONCLUSION

The burden of neonatal sepsis at a selected children's hospital of Zambia is relatively high. The study has found that an increase in duration of empirical treatment is predictive of antibiotic resistance commonly for *Enterobacter spp* followed by *E. coli spp* among the gram negative bacilli and *Staphylococcus spp* among the Gram positive cocci. Most common resistant antibiotics belonged to penicillins and third generation cephalosporins. The findings in this study suggests need for faster bacterial culture diagnosis to avoid unnecessary empirical treatment and continuous surveillance of susceptibility pattern should be essential component of neonatal care.

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