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Neonatal Sepsis and Antibacterial Profile in Neonates at a Selected Children's Hospital in Zambia

Jonathan Gwasupika

Ministry of Health, Tropical Diseases Research Centre, Departments of Clinical Sciences and Public Health
Email: *gwagwejo[at]gmail.com*

Abstract: ***Background: Neonatal sepsis is a common condition among neonates particularly in developing countries. Treatment of neonatal sepsis iswith 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 investigating neonatal sepsis and antibacterial profile at a selectedchildren'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. Results: Out of the 172 blood cultures analysed, 61.0% (105/172) were male admissions affected with 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. Conclusion: Early detection of bacteria causing sepsis and sensitive antibiotics via blood culture and drug sensitivity testing would probably reduce the rate of antibiotic resistance.***

Keywords: Antibiotic resistance, neonatal sepsis, Bacteria

1. Introduction

On a global scale, a rise in antibiotic resistant organisms is considered a public health concern. Annually, more than one million neonatal mortalities may be attributed to severe infections in neonates worldwide (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 feature 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).Microorganisms differ from place to place and due to inadequate laboratory resources in most resource-poor settings such as those commonly seen in sub-Saharan African countries, diagnosis of neonatal sepsis is mostly concluded clinically and treatment is not based on susceptibility pattern cultured microorganisms causing infections (3, 7). 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 gentamycin. 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 we opted to investigate the common bacteria for neonatal sepsis and antibacterial profile in neonates at a selected Children's Hospitalin Zambia.

2. Materials and Methods

We conducted a retrospective cross-sectional study at a selected children's hospital known as Arthur Davison children 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 a day are admitted to neonatal intensive care unit (NICU) at ADCH 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 were 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 (Company, city, country) 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, the median and interquartile ranges were used for skewed data. Frequency and percentages were used to report categorical data. Figures and tables were used to describe proportions. STATA software, version 14 SE (STATA Corp., College Station, Texas, USA) was used to come up with figures.

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.

3. Results and Discussion

This study was set out to investigate neonatal sepsis and antibacterial profile in neonates at Arthur Davison children's Hospital (ADCH) in Ndola, Zambia. This study found that about 61.0% (105/172) male neonates were admitted with suspected neonatal sepsis. 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.

Demographic and clinical characteristics of participants

Neonatal sepsis is regarded as the leading cause of mortality and morbidity in the neonatal intensive care unit (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. 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). This is shown in table 1.

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

Variable	Category	Frequency (%)
Sex	Male	105 (61.0)
	Female	67 (39.0)
Age at admission (days)	≤3	67 (39.0)
	>3	105 (61.0)
Blood culture result	Positive	120 (69.8)
	Negative	52 (30.2)
Gram stain	Negative bacilli	103 (85.8)
	Positive cocci	17 (14.2)
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 associated with neonatal sepsis

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). Figure 1 shows common isolated bacteria.

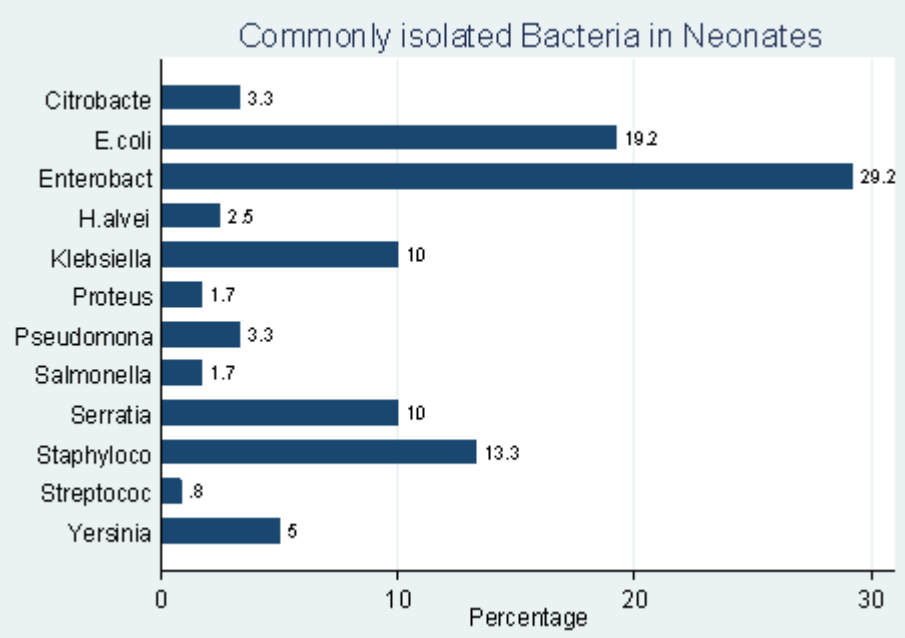


Figure 1: Proportion of commonly isolated bacteria in neonates with neonatal sepsis

Neonates who presented with late onset sepsis had a relatively high culture yield and were mainly associated with Gram negative Enterobacteriacae. This is similar to studies done in Ethiopia (21, 22) and Egypt (3).This finding could be attributed to blood culture results of neonates with early onset sepsis might have been affected by maternal antibiotics administration during labour and delivery (23). This study did not report any blood culture growth for group B streptococcus (GBS) which is also in agreement with a study done by Abebe (21). This finding could be explained by the fact that GBS is purely acquired through vertical transmission from the mother during labour and delivery as most motherswith risk of GBS colonization receive penicillin antibiotics for which this species of bacteria remain invariably sensitive (24).Among the Enterobacteriaceae family, *Enterobacter spp* was the most common cause of both late onset sepsis and early onset sepsis followed by *E. coli spp*. However, *Yersinia spp* was noted to cause more of early onset sepsis (66.67%) as compared to late onset sepsis (33.33%).

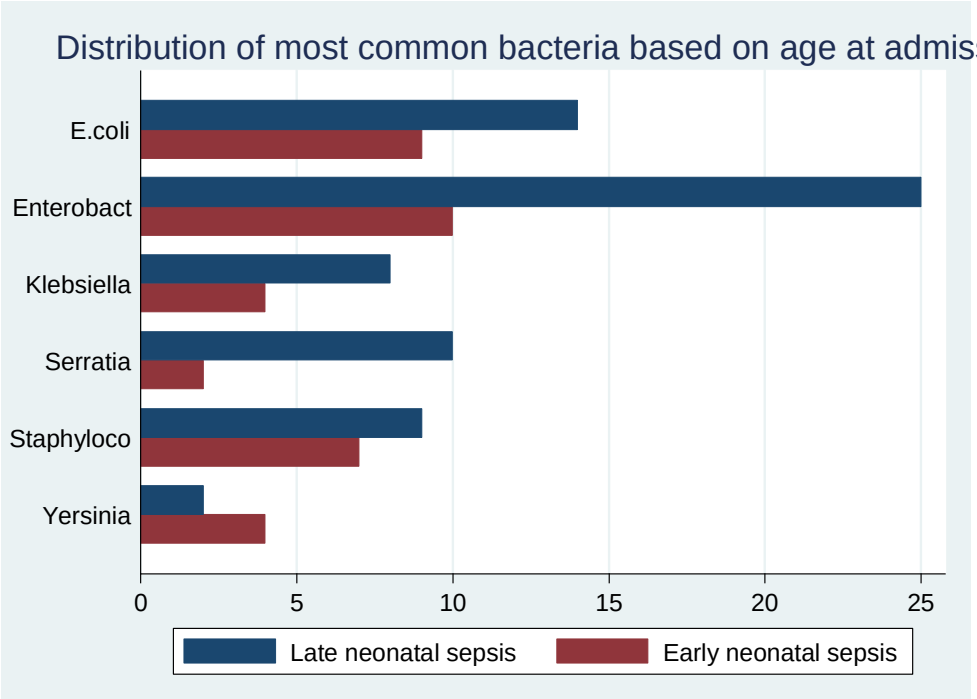
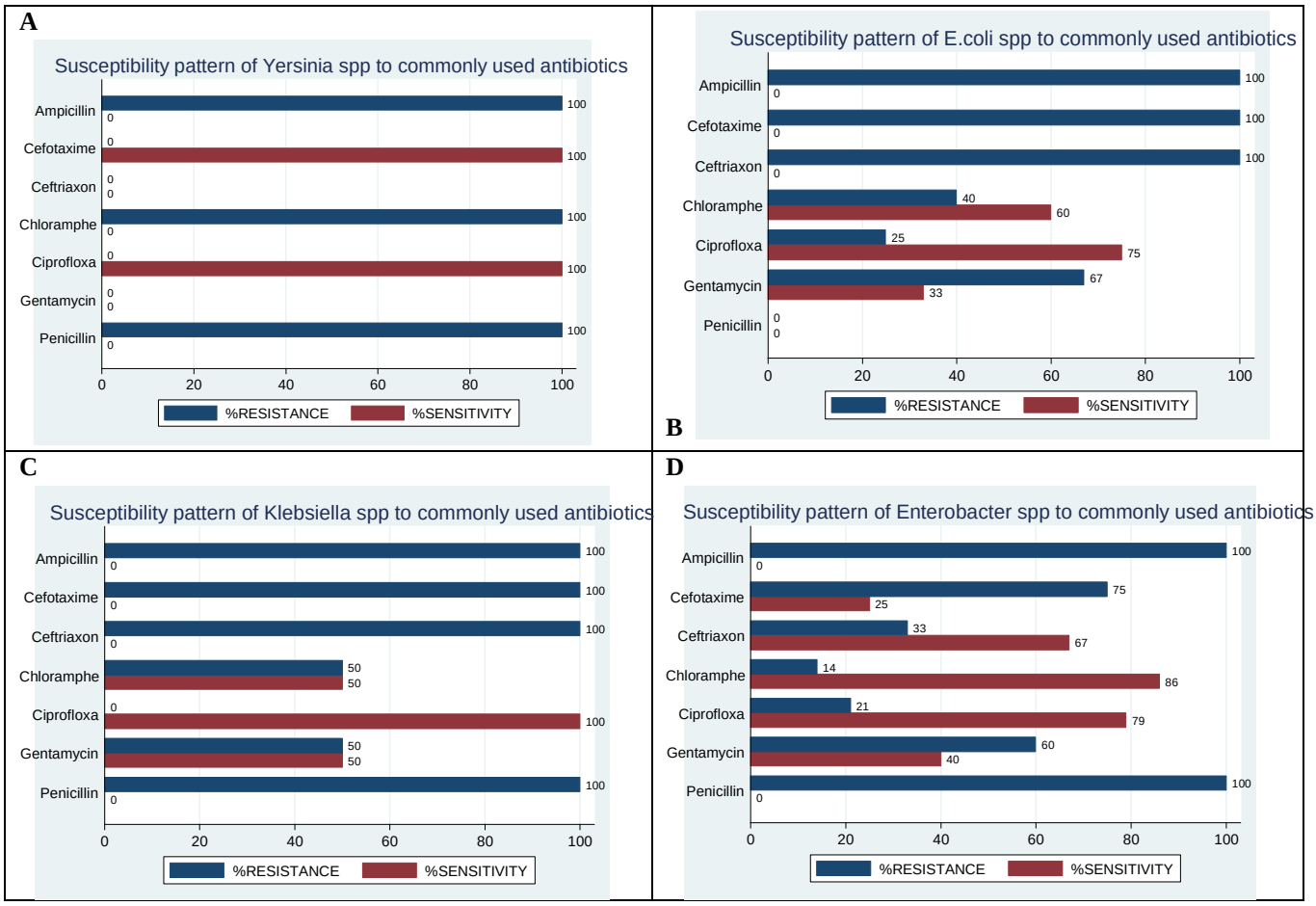


Figure 2: Distribution of most common bacteria based on age at admission

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

Antibiotics belonging to the Penicillin group such as Ampicillin, Penicillin G, 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, 25). Other commonly used antibiotics that showed resistance were Gentamycin (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 Gentamycin or third generation cephalosporins (26). This prolonged duration of antibiotic use could have led to bacteria copying strategy of action thus causing antibiotics to be inactive (25). However, most of the isolated bacteria were sensitive to ciprofloxacin and chloramphenicol, similar to studies done by Ogundare et al., (25) and Kabwe et al., (11). These studies did not show the sensitivity of chloramphenicol. Ogundare et al., (25) showed that cefotaxime and ceftriaxone were sensitive which was different from this study Figure 3 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. 3 D) *followed by E. coli spp* (fig. 3 B) *and Klebsiella spp* (fig. 3 C). Antibiotics that were tested for susceptibility against *Yersinia spp*, (fig. 3 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 3 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 chloramphenicaol and cefotaxime were seen to be 100% towards Serratia spp (fig 3 F).



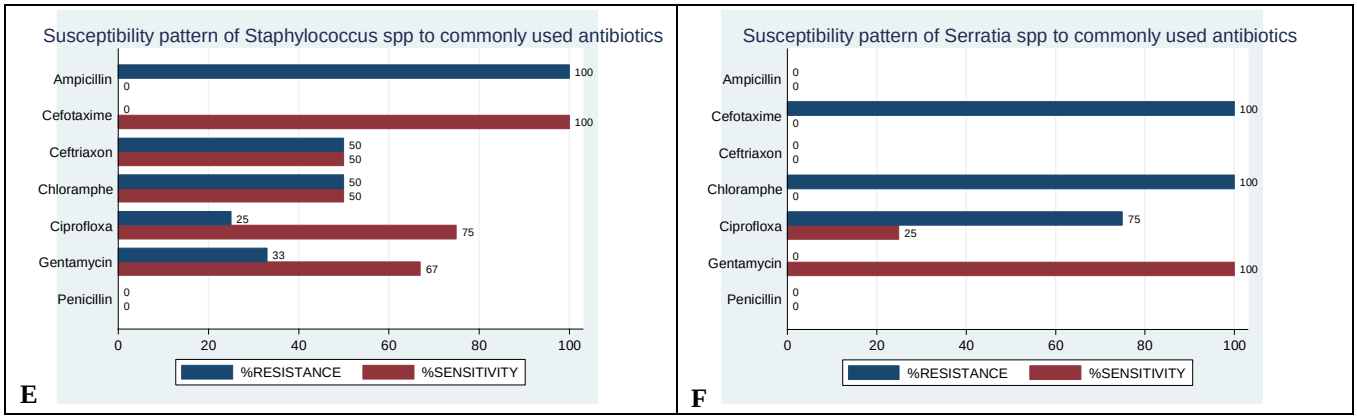


Figure 3: Susceptibility pattern of each commonly isolated bacteria to commonly used antibiotics

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. 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 may reflect the situation at the institution as limitations such as level degree of missingness, were taken into consideration at all costs.

4. Conclusion

The prevalence of positive blood culture result was 69.8%. Majority of neonates with culture positive presented with late onset sepsis. Gram negative bacilli from the Enterobacteriaceae family were noted to be the most common cause of neonatal sepsis with Enterobacter spp being the common causative agent followed by E. coli spp whereas Staphylococcus spp was the most common cause of neonatal sepsis among the Gram positive cocci. Most common resistant antibiotics belonging to penicillins and third generation cephalosporins. 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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