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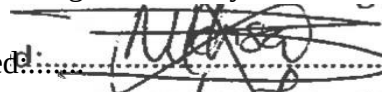
EPIDEMIOLOGY OF BACTERIAL BLOODSTREAM INFECTIONS IN VERY LOW BIRTH WEIGHT NEONATES AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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Declaration

I, Moses Matlhadisa declare that the research report is my own work and any publication used have been appropriately referenced. This research report is submitted for the Degree of Master of Medicine in Paediatrics at the University of the Witwatersrand. It has not been submitted for a degree or to any another university.

Signed: 

Date: 07/05/20

Dedication

I would like to dedicate this research work to my lovely family, Nomsa and Karabo for all their support and encouragement.

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I would to thank my supervisors Prof D.E Ballot and Dr V Chibabhai for their support and guidance during this research project. I am very grateful for their valuable time taken to assist with the research.

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List of abbreviations

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital
LIMC: Low-middle income countries
BSI: Blood stream infection
EoNS: Early onset neonatal sepsis
LoNS: Late onset neonatal sepsis
VLBW: Very low birth weight
NEC: Necrotising enterocolitis
HIV: Human immunodeficiency virus
CoNS: Coagulase negative staphylococcus
GNB: Gram negative bacilli
ESBL: Extended spectrum beta Lactamase
MRSA: Methicillin resistance staphylococcus aureus
MDR: Multi-drug resistant

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Abstract

Introduction: Very low birth weight (VLBW) neonates are at a higher risk of neonatal sepsis because of immature immune system and prolonged hospitalisation. The pattern of causative pathogens changes with time therefore frequent surveillance remains essential.

Objectives: To review bacterial organisms causing bloodstream infections and their associated antimicrobial susceptibility pattern.

Methods: A retrospective observational study between 1st January 2016 and 31st December 2016 was performed. The study population included all VLBW neonates with blood culture proven infection who were admitted to the neonatal unit at Charlotte Maxeke Academic Johannesburg Hospital (CMJAH).

Results: A total of 184/479 (38.4%) neonates had culture proven bacterial sepsis accounting for a total of 206 episodes of bloodstream infection (BSI). There were twenty-two (10.7%) episodes of early onset sepsis (EONS) and 184 (89.3%) late onset sepsis (LONS) respectively. Gram positive organisms accounted for the majority of isolates with c*oagulase negative Staphylococci* (CoNS) being the commonest pathogen in EONS at 68% and LONS at 35% respectively. The retrospective nature of the study meant that it was not possible to determine if CoNS were contaminants or pathogens. There was no case of *Streptococcus agalactiae* in the EONS. The number of multidrug resistant organisms was more common in LONS than EONS with extended beta lactamase producers in 20% of gram negatives. The majority of *S. aureus* isolated in LONS were methicillin resistant staphylococcus aureus (MRSA).
Accordingly, the overall susceptibility to the first line antimicrobials is low.

Conclusion: The current first line therapy does not provide adequate cover. There is poor susceptibility to ampicillin by most pathogens but it is still remains an antibiotic of choice for EONS. LONS is still more predominant than EONS. Meropenem and vancomycin are suitable option for LONS.
Keywords: Neonate, sepsis, bacterial, very low birthweight, bloodstream infections
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Background

Sepsis is a major cause of morbidity and mortality neonates with a higher incidence reported in low-middle income countries (LMIC) than in higher income countries. In 2019, 47% of deaths in children under the age of five years occurred in the neonatal period and the majority are due to infection (1, 2). The pattern of causative organisms continually changes, with increasing prevalence of resistant organisms. It is therefore necessary to regularly review organisms causing neonatal sepsis and their antimicrobial susceptibility to guide appropriate therapy. (3).

Neonatal sepsis is defined as a clinical syndrome, manifested by systemic signs of infection with or without isolated pathogen on culture. Clinical diagnosis is often very difficult because neonates present with nonspecific signs and symptoms. The major clinical features include fever, bradycardia, temperature instability, glucose instability, apnoea attacks, and respiratory distress. In severe cases of sepsis patients will present with signs of shock mainly skin colour changes and poor perfusion. While laboratory confirmation requires time, there can never be any justification to delay treatment because that will result in avoidable mortality and morbidity. Appropriate empiric antimicrobial is guided by continuous surveillance of pathogens and their susceptibility to antibiotics used (4).

Early onset neonatal sepsis (EONS) occurs within the first 72 hours of life. Bhat et al reviewed bacterial isolates of EONS in India while Akindoline et al reported on EONS in Nigeria (3, 5). The pathogens isolated in these two studies were different, therefore highlighting the need to have local current information about pathogens and their antimicrobial susceptibility pattern to guide empiric antibiotic therapy of choice. In general, the organisms causing EONS are usually acquired from the mother before or during delivery, whereas organisms causing late onset neonatal sepsis are acquired from the environment or health care workers. The pattern of pathogens is changing with more cases of *K. pneumoniae* and *E. coli* been reported with cases

of early onset neonatal sepsis (6, 7). The rate of *S agalactiae* infections have been substantially reduced with antibiotic-based prevention strategies in resource-rich countries (7).

Late onset neonatal sepsis (LONS) occurs after the first 72 hours of life until the end of the neonatal period (28 days of life) and is generally associated with different pathogens and different risk factors to that of EONS(8) . Pathogens isolated in LONS are frequently resistant to many antimicrobial agents. The organisms are mainly gram negatives, *Klebsiella pneumoniae,* and *Escherichia. coli* are some of the pathogens implicated (8).

In South Africa, Ballot et al found that coagulase negative staphylococcus (*CoNS)* was the most common isolate in LONS (19% of all positive culture results) (4). This was followed by *K. pneumoniae* at 12.1% and *Acinetobacter baumannii* at 10% respectively (3). In a study done in Taiwan which looked at both EONS and LONS, gram-positive and gram-negative pathogens were isolated with nearly equal frequency (9) .

There has been an increase in the number of multidrug-resistant (MDR) pathogens causing neonatal sepsis over time, with extended spectrum beta lactamase (ESBL) *Klebsiella species*, *Acinetobacter baumannii* and carbapenem resistant Enterobacterales (CRE) becoming increasingly common isolates in the neonatal period (4). These MDR pathogens are associated with a high mortality rate. The World Health Organisation (WHO) recommends ampicillin (or penicillin; cloxacillin if staphylococcus infection is suspected) plus gentamicin for empiric treatment of neonates with suspected clinical sepsis (9, 10) . The extensive use of antibiotics has resulted in emergence of resistant bacterial strains such as gentamicin resistant *Klebsiella* species, 3rd generation cephalosporins resistant gram negatives and *methicillin resistant Staphylococcus aureus* (MRSA) (11). The local study by Ballot et al found that 86% of *CoNS* and 69% of *S. aureus* were MRSA, while 65% of *K. pneumoniae* were ESBL producers (4).

Ullah et al in their Pakistan study found imipenem to be effective against all bacterial isolates and remained the drug of choice for treatment of neonatal sepsis (10, 12).

Therefore, with this context in mind, the aim of this research project was to investigate the epidemiology of bacterial neonatal sepsis (early and late onset) and the patterns of bacterial pathogens including their antimicrobial susceptibility in very low birth weight infants.

Subjects and methods

This was retrospective review of very low birth weight (VLBW) neonates with bacterial sepsis who were admitted to the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 01 January 2016 and 31 December 2016. . Neonates with culture proven bacterial bloodstream infections were included. The exclusion criteria were neonates with unobtainable records and positive cultures with commensal organisms or fungi. The following organisms were regarded as contaminants: *Micrococcus species, Bacillus species and Corynebacterium species* [4]. Data captured from the neonatal computer database included demographic and clinical characteristics of the neonates, bacterial isolates and antimicrobial sensitivity.

Empiric antibiotic therapy for EONS during the study period was ampicillin and gentamicin, while piperacillin/ tazobactam and amikacin or meropenem and vancomycin were used empirically for LOS. Antibiotic therapy and positive cultures were reviewed in consultation with a microbiologist and antibiotics were tailored according to the sensitivity of the organisms cultured.

Preterm and VLBW neonates have immature immune systems and are therefore at increased risk of sepsis.(13). Coagulase negative Staphylococci have been described as the most common

pathogen in high income countries (14) and, more recently, as the most common isolate in both EONS and LONS in low to middle income countries (15). However, a proportion of CONS isolated in blood cultures from sick VLBW neonates may be contaminants (16). In this retrospective review, it was not possible to establish if CoNS isolates indicated clinical infection or contamination, as a result CoNS isolates were considered to be clinically significant.

Blood culture bottles were incubated in the bacTAlert (bioMerieux, Marcy L-Etoile) automated blood culture system for a period of seven days. Once sufficient growth was obtained, identification and susceptibility testing were performed using the Vitek 2® (bioMerieux, Marcy L-Etoile) automated identification and susceptibility testing system. Clinical Laboratory Standard Institute Guidelines (CLSI) for the relevant year were used to interpret the susceptibility results.

Ethics

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Certificate number M170407). Data was de-identified to maintain patient confidentiality.

Statistical analysis

The statistical analysis of the results was performed using SPSS version 24 (IBM). Categorical variables were described as frequencies and percentages. Continuous variables were described using means and standard deviation.

Results

The study population

There was a total of 479 very low birth weight (VLBW) neonates who were admitted to the neonatal unit over the study period from 01 January 2016 till 31 December 2016. One hundred and seventy-three neonates (36.1 %) developed blood culture proven bacterial sepsis. The mean birth weight of neonates with BSI was 1109 grams (SD 236.1grams), the mean gestational age was 29 weeks (SD 2weeks) and the mean duration of stay was 32 days (SD 25days). Additional characteristics of the VLBW neonates are shown in Table 1.

Table 1. Clinical data of very low birth weight babies with culture proven bacterial sepsis

Characteristics	Number (173) (%)
Female	78 (45.0)
HIV exposure	68 (39.3)
Antenatal care	132 (76.3)
Outcome (Death)	50 (28.9)
Normal vaginal delivery	79 (45.7)
NCPAP	126 (72.8)
IPPV	66 (38.1)
NEC	17 (9.8)

HIV: Human immunodeficiency virus, NCPAP: Nasal continuous positive airway pressure, IPPV:
Intermittent positive pressure ventilation, NEC: Necrotizing enterocolitis

Blood stream infections

There were two hundred and six episodes of BSI in 173 VLBW neonates, 23 VLBW neonates had multiple episodes of BSI (See Table 2). Twenty-two episodes (10.7%) BSI occurred within the early neonatal period compared to the 184 episodes (89.2%) that occurred during the late neonatal period.

Table 2: Episodes of Bacterial bloodstream infection per very low birth weight neonate

Episodes of infections	Number of neonates
One	150
Two	16
Three	5
Four	1
Five	1

Pathogens isolated

Gram positive and gram negative isolates are shown in Table 3.

Table 3: The pathogens isolated on blood during the study period based on the gram stain findings.

Organisms	(Early onset sepsis) Number (%)	(Late onset sepsis) Number (%)
Gram positive organisms		
Coagulase negative staphylococcus	15(68.2)	76(41.3) 13(7.1)
Streptococcus agalactiae	0	10(5.4)
Staphylococcus aureus	2(9.1)	8(4.3)
Enterococcus faecalis	0	6(3.3)
Enterococcus faecium	0	1(0.5)
Enterococcus species	0	1(0.5)
Streptococcus viridans	0	
Gram negative organisms		
Klebsiella pneumoniae	1(4.5)	33(17.9)
Acinetobacter baumannii	3 (13.6)	16(8.7)
Escherichia coli	1(4.5)	12(6.5) 2(1.1)
Serratia marcescens Pseudomonas aeuriginosa	0	1(0.5)
	0	1(0.5)
Burkholderia cepacian	0	1(0.5)
Enterobacter aerogenes	0	

Early onset neonatal sepsis

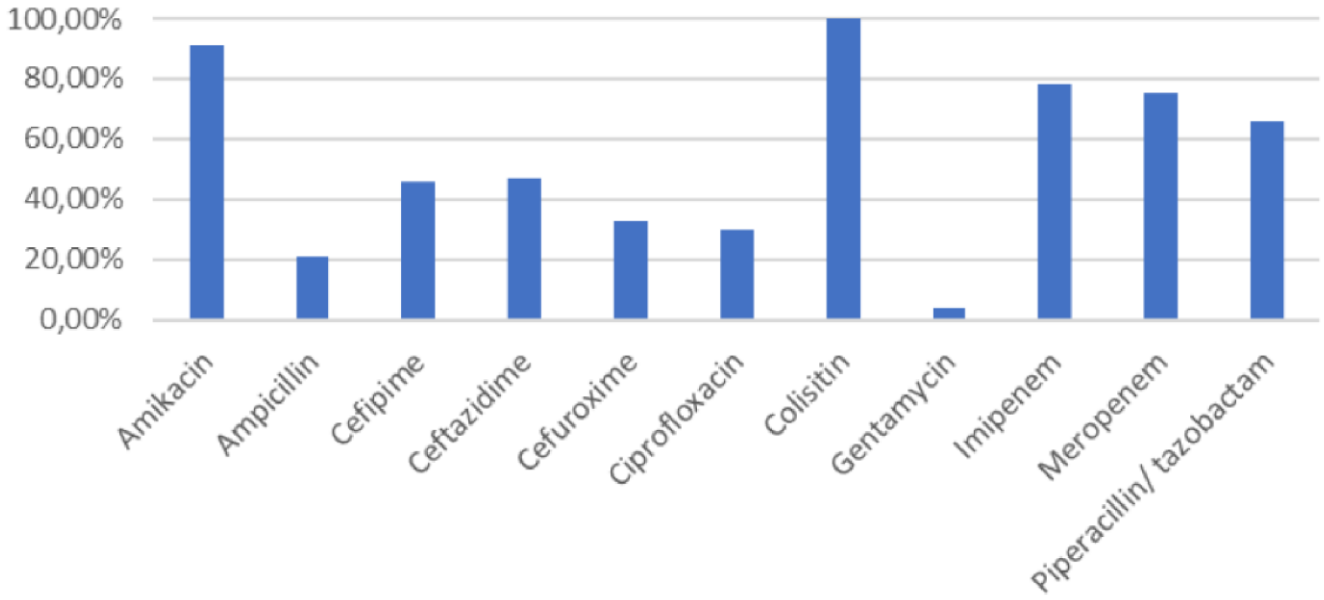
There was a total of 22 BSI with a high prevalence of gram-positive organisms (77.3%) as shown in Table 1. There were no cases of *S. agalactiae* isolated during the study period. With regard to empiric antibiotic therapy for EONS, all five gram negative organisms were resistant

to ampicillin and 2/5 were resistant to gentamicin. The overall susceptibility of CoNS infections to first line antibiotics was found to be only 10.7%. The *A. baumannii* infections were all susceptible to colistin but showed a low susceptibility of only 33% to meropenem.. There was one case of MRSA infection which was found to be susceptible to vancomycin. The other remaining two isolates were *K. pneumoniae* and *E. coli* infections respectively which were all susceptible to amikacin and meropenem.

Late onset neonatal sepsis

There was a total of 184 bacterial blood stream infections in LONS. The most common isolate was CoNS (41,3%), followed by *K. pneumoniae* (17,9%). Antimicrobial sensitivity of the isolated gram negative organisms is shown in Figure 1. Of note, the majority of gram negative organisms were susceptible to empiric LONS antibiotic therapy – namely amikacin (91.3%) meropenem (73.9%) and piperacillin/tazobactam (66.2%) There were 12.5% (23/184) cases of ESBL infections.

Figure 1. Antimicrobial sensitivity (%) of gram negative organisms isolated from very low birth weight neonates



There were 5.4% (10/184) cases of LONS due to MRSA. There were 13/184 cases (7.1%) of *S. agalactaiae*, which were all susceptible to ampicillin/penicillin, and vancomycin.

Discussion

This study showed that more than one third of VLBW neonates admitted to the study unit had culture proven blood stream infection (BSI). Late onset neonatal sepsis (LONS) was found to be more prevalent than early onset neonatal sepsis (EONS) in a ratio of almost 9:1. These findings are similar to an earlier review conducted in the same unit (4). VLBW neonates are at increased risk of sepsis because of their underdeveloped immunity, need for central venous access and prolonged hospitalisation (9, 17).

In the present study, the most common isolate in both EONS and LONS was CoNS. This is in keeping with other reports from LMICS (15) and is similar to findings in an earlier studies in the same unit (4, 18). However, it is difficult to determine which CoNS isolates in ill neonates are actual pathogens as opposed to contaminants (16). Our findings are in contrast to an Indian study where gram negative organisms were more prevalent in EONS; *P. aeruginosa* was found to be the commonest pathogen followed by *A. baumannii* .(19). Recent studies in many developing countries found that in addition to the fact that most of the organisms are gram negative, there is generally very low susceptibility to ampicillin (4). In other studies from low to middle income countries such as Nigeria and India, CoNS was often excluded from the analysis because of difficulty in proving that it is the organism causing the sepsis (19).

There was one case of MRSA in the EONS, which was found to be sensitive to vancomycin. It is worth highlighting that there was no case of ESBL in the EONS. There was a 100% resistance to ampicillin in the EONS group while there was a susceptibility of 71.4% to gentamicin. These findings suggest a review of first line empiric antibiotic therapy for EONS, with possible use of amikacin as a first line agent for gram negative organisms.

There were no cases of EONS due to *S. agalactaiae* in the current study. This is in contrast to the previous study in the same unit where seven cases of *S. agalactaiae* were isolated in EONS(4). However, *S. agalactaiae* was found in 7.1% of isolates in LONS in the current study and all were sensitive to ampicillin. Therefore, ampicillin remains a reasonable choice for antibiotic therapy of *S. agalactaiae*.

The gram-negatives were the predominant isolate in LONS when CoNS is excluded from our analysis. *K. pneumoniae* was the commonest gram-negative accounting for 17.9% of the total infections. There were twenty-four ESBL isolates in the LONS group, which accounted for 13% of total infections. Both the number of *K. pneumoniae* isolates and ESBL producers are more common than in the previous review from the same unit (4). The *K. pneumoniae* ESBL isolates are intrinsically resistant to ampicillin. The majority were sensitive to piperacillin/tazobactam, amikacin and meropenem, therefore these antibiotics remain a good choice for empiric therapy of LONS. There was a higher proportion of ESBL isolates among *K. pneumoniae* (92%) compared to other gram-negative organisms. The predilection for ESBL production by *K. pneumoniae* has been noted by other researchers previously (11). The other two cases of ESBL were *S. marcescens* and *Enterobacter spp.* which were both susceptible to amikacin.

There were nine cases of MRSA in the *S. aureus* group. Only one case was susceptible to gentamicin amongst other antibiotics. The majority of *S. aureus* isolated in the LONS group were MRSA. The similar high prevalence has been reported in other studies in LMIC (6, 20).

It is well known that with prolonged hospitalisation the risk of nosocomial infection is increased (5, 17). Infections with *A. baumannii* were also high accounting for 8.7% of the total infections with three infections in the EONS compared to the sixteen in the LONS. It is important to highlight that all *A. baumannii* isolates were in LONS in the previous audit from the same unit (4). All the isolates were susceptible to colistin followed by ciprofloxacin at 43.7% and low

susceptibility to meropenem and cefepime at 18.7%. We did not find any case of pan-resistant *A. baumannii* in our population during the period of the study.

Infections with *E. coli* were the third commonest gram-negative infections accounting for 6.5% of the total infections and all the isolates showed 100% susceptibility to amikacin and cefotaxime. This is similar to the previous report from the same unit (4). Some researchers have found the *E. coli* to be the commonest gram-negative causing neonatal sepsis because of its association with colonisation of the genital urinary tract system (5). *Enterococcus* species were also common gram-positive isolates. The susceptibility of *E. faecalis* and *E. faecium* to ampicillin at 76.9%.

The pattern of neonatal sepsis in the CMJAH neonatal unit has changed marginally between 2010 and 2016, with an increase in *K. pneumoniae* ESBL producers. CoNS remains the most common isolate in both EONS and LONS. Of concern, is the isolation of resistant gram negative organisms in EONS. Empiric antibiotic therapy for EONS should possibly be changed to amikacin rather than gentamicin, but other antibiotic protocols remain appropriate.

Study limitations

The study was a retrospective review. There might have been over-reporting in this study due to duplicate isolates. Limited clinical and laboratory data was collected in this retrospective review, so the significance of CoNS isolates could not be determined. Neonatal sepsis was defined by a positive blood culture , septic neonates with negative blood cultures were not included in this study.

Conclusion

Neonatal BSI is a common problem at CMJAH neonatal unit. In view of the high prevalence of LONS, the importance of strict infection control measures like hand-washing and barrier nursing cannot be overemphasised. The antimicrobial susceptibility of pathogens to our first

line empiric antibiotics, ampicillin and gentamicin was found to be very low therefore amikacin might be a better aminoglycoside of choice. We recommend that for multi-drug resistant (MDR) gram-negative isolates, meropenem should be initiated while colistin is reserved for resistant *A. baumannii* sepsis. Linezolid and vancomycin are the best option for MDR grampositive isolates. Ampicillin is still the antibiotic of choice for treatment of *S. agalactiae* infection. As part of good antibiotic stewardship, it is recommended that antimicrobials should be guided by the blood culture results with susceptibility testing. In view of the findings of the BSI audits in CMJAH neonatal unit, continuous surveillance is strongly recommended to guide the choice of empiric antibiotic therapy.

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Research Protocol

TITLE

Epidemiology of bacterial bloodstream infections in Neonates at Charlotte Maxeke Johannesburg Academic Hospital

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MMed Paediatrics

Supervisor: Prof D. Ballot
Supervisor: Dr V.Chibabhai

INTRODUCTION

Background

Neonatal sepsis is a major cause of neonatal mortality with higher incidence reported in developing countries than developed countries. It is estimated that 1 million deaths each year are attributed to infections acquired during the neonatal period. Other authors have estimated neonatal mortality rate to be 44 per 1000 live births which is four times the rate of developed nations(21).

Burden of neonatal sepsis

In developing countries, there is wide variation in the incidence from one country to another and within a country there is variation between health care facilities. Authors in Pakistan have reported a rate of 5.6 per 1000 live births in a hospital based study compared to a rate of 54.9 per 1000 live births in a hospital based study in Nigeria(22). The incidence differs between the hospital based studies versus community based studies with very high incidence documented at the community levels due to various reasons including poor access to health care facilities and delayed presentation to hospitals(23, 24).

There is a general agreement among researchers that neonatal sepsis carries a huge burden in developing countries and more research is needed to better understand this syndrome and shed light on its management(25).

Definitions

Neonatal sepsis is defined as a clinical syndrome, manifested by systemic signs of infection and isolation of a bacterial pathogen from the bloodstream of an infant younger than 28 days old (22). Clinical diagnosis is often very difficult because neonates present with nonspecific signs and symptoms. The major clinical features will include fever, bradycardia, temperature instability, glucose instability, apnoea attacks, and respiratory distress and in severe cases patients will present with signs of shock including skin colour changes and poor perfusion. These features have been reported with different prevalence with Jiang et al reporting fever in 38% of cases. While laboratory diagnosis or confirmation requires time, empiric treatment is needed until sepsis has been ruled out. There can never be any justification to delay treatment because that will result in avoidable mortality and morbidity. It is this need of appropriate empiric treatment that is relevant to our settings that necessitates continuous surveillance of pathogens and their susceptibility to antibiotics used(26).

Early onset neonatal sepsis

The early onset neonatal sepsis occurs within the first 72 hours of life(22). The infection is caused by bacterial, fungal and viral infections. Bhat et al looked at bacterial isolates of early onset sepsis in India while Akindoline et al looked at a similar problem in Nigeria(22, 27). The pathogens isolated in the two studies were different, indicating the need to have local current information about pathogens and their antimicrobial sensitivity to guide empiric antibiotic therapy of choice that is appropriate for the settings. In general the organisms causing early onset sepsis are usually acquired from the mother before or during delivery, whereas organisms causing late onset sepsis are acquired from the environment. Early onset neonatal sepsis is associated with maternal fever, urinary tract infections, and foul smelling vaginal discharge. The pattern of pathogens is changing with more cases of *Klebsiella pneumoniae* and *Escherichia coli* been reported with cases of early onset neonatal sepsis (26-28). In the developed world, the rate of group B *Streptococcus* (GBS) infections has been reduced drastically from interventions directed at eradicating maternal carriage of GBS before delivery.

Late onset neonatal sepsis

The late onset neonatal sepsis occurs after the first 72 hours of life until the end of neonatal period (28 days of life) and it is generally associated with different pathogens and different risk factors to that of early onset neonatal sepsis(29). Pathogens isolated in late onset sepsis are frequently resistant to many antimicrobial agents. Neonates acquire these pathogens from the

environment, which are transmitted by parents or health care professionals. The organisms are mainly gram negatives, *K. pneumoniae,* and *E.coli* are some of the pathogens implicated. The risk factors that are strongly associated with late onset neonatal sepsis include prolonged rupture of membranes, emergency cesarean section, male sex and meconium stained liquor (MSL)(28). In Tanzania, MSL was found to be associated with high risk of sepsis but no similar findings were observed in developed countries(30). Seale et al looked at maternal colonisation with *Streptococcus agalactiae* as a risk factor for neonatal sepsis. Because of previously documented low carriage of this organism in many African settings, it was not found to be a significant risk factor(28).

Factors associated with neonatal sepsis, an important cause of childhood mortality are poorly described in Africa(31). Knowledge of risk factors predisposing to neonatal sepsis can help reduce the burden of this problem by enabling early detection of infection and initiation of appropriate antibiotics. As previously highlighted neonates often present with atypical nonspecific clinical features which can delay diagnosis and initiating treatment.

It is standard practice that all neonates with suspected sepsis will have blood cultures taken and started on empiric treatment until infection has been ruled out. In our unit, empiric treatment of ampicillin and gentamicin is initiated for early onset neonatal sepsis while awaiting blood culture results. Antibiotics are changed based on the microbiology report with the susceptibility of the pathogen cultured. The second line antibiotics for late onset neonatal sepsis are carbepenems and vancomycin which are started in consultation with the microbiology team.

Screening of GBS colonization and intrapartum antibiotic prophylaxis is already implemented in developed countries with good outcome. In our setting, we advocate for antibiotics only if indicated such as when there is a history of prolonged rupture of membranes, signs of urinary tract infection, clinical features of chorioamnionitis, fever and foul smelling. Intrapartum antibiotic prophylaxis (IAP) has been proved to be effective in preventing early onset neonatal sepsis caused by group B streptococcus even in our setting as a developing country(31). The low birth weight and gestational age, preterm deliveries are important risk factors for neonatal sepsis. Schrag et al showed that low birth weight and preterm delivery were the two most important risk factors for sepsis in their trial(31).

Antibiotic susceptibility amongst pathogens differs and this pattern changes over time from one facility to another. Neonates are started on empiric treatment once an assessment of suspected

neonatal sepsis has been made. This is based on evidence of clinical features pointing towards infection and/or blood results with abnormal white cell count or raised C-reactive protein. Therefore not all cases of suspected sepsis will yield positive blood culture results. Antimicrobial therapy is adjusted according to the pathogens isolated on blood culture. In cases where there is no bacterial growth and the neonates condition is improving, antibiotics are discontinued within 72 hours.

This research will focus only on culture proven bacterial bloodstream infections. It is important to highlight that microbiology isolates are different from one study to another with positive cultures accounting for about 10% of collected samples. In South Africa, Ballot et al found that coagulase- negative *Staphylococcus* was the most common isolate in late onset sepsis (19% of all positive culture results). This was followed by *K. pnuemoniae* at 12.1% and *Acinetobacter baumannii* at 10% respectively(26). A trial done at another facility in the same province found group B *Streptococcus* to be the commonest pathogen (10% of culture confirmed neonatal sepsis**)**. *E. coli* was found to be the leading cause of late onset neonatal sepsis(32). These findings further highlight the variation in pathogens within the same province and emphasise the need for current local data to guide empiric antimicrobial therapy.

A Nigerian study looking at pathogens causing early onset neonatal sepsis found that *Staphylococcus aureus* is the commonest pathogens with no cases of Group B *Streptococcus* infection(22). In a study done in Taiwan which looked at both early and late onset sepsis, gram positive and gram negative pathogens were isolated with nearly equal frequency(29). Coagulase- negative *Staphylococcus* was also found to be the commonest pathogen in that study.

There has been an increase in a number of multidrug-resistant (MDR) pathogens causing neonatal sepsis over time, with extended spectrum beta lactamase (ESBL) *Klebsiella species*, *Acinetobacter* and carbepenem resistant enterobacteracaea becoming increasingly common isolates in neonatal patients(24). These MDR pathogens are associated with high mortality. Pathogens associated with late onset sepsis were found to be associated with high mortality and antibiotic resistance(21, 26).

The world health organisation (WHO) recommends ampicillin (or penicillin; cloxacillin if staphylococcus infection is suspected) plus gentamicin for empiric treatment of neonates with suspected clinical sepsis(33). The extensive use of antibiotics has resulted in emergence of

resistant bacterial strains such as gentamicin resistant *Klebsiella* species, 3rd generation cephalosporins resistant gram negatives and methicillin resistant *staphylococcus aureus*(34). The local study by Ballot et al found that 86% of Coagulase negative *staphylococcus* and 69% of *S. aureus* were methicillin resistant, while 65% of *K. pneumoniae* were ESBL producers (26). These findings along with antimicrobial susceptibility pattern reported in Egypt by Fahmey et al bring into question the evidence of the WHO recommendation on antibiotics choice and highlight the need for more data relevant to our setting(34). Most of the trial looking at antimicrobial susceptibility reports on many antibiotics profile. It is important to mention that the above quoted studies reported no cases of vancomycin resistant gram positive organisms(26, 34).

The beta-lactam antibiotics are reported to be prone to rapid evolvement of bacterial resistance and should be reserved for treatment of severe or resistant infections. Most studies report high susceptibility to carbepenem, in a study done locally there was no case of carbepenem resistant *enterobacteriaceae(26).* The Egyptian study reported a high susceptibility of up to 91%. Ullah et al in their Pakistan study found imipenem to be effective against all bacterial isolates and remained the prime drug of choice for treatment of neonatal sepsis(34, 35). As antimicrobial resistance is becoming a major issue globally, the use of standardized definitions becomes very important to allow collection of reliable epidemiological surveillance data that can be compared across healthcare settings and between countries(36).

The following definitions will be used as adopted from Magiorakos et al: Multi-drug resistant (MDR) is defined as non-susceptibility to at least one agent in three or more antimicrobial categories. Extensive drug-resistant (XDR) is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories. Pandrug-resistant (PDR) is defined as nonsusceptibility to all agents in all antimicrobial categories(36).

Therefore, with this context in mind, the aim of this research project is to investigate the current incidence of bacterial neonatal sepsis (early and late onset) and the patterns of bacterial pathogens including their susceptibility.

STUDY OBJECTIVES

1. To determine the incidence of bacterial neonatal sepsis at Charlotte Maxeke Johannesburg Academic Hospital, stratified by early and late onset

2. To determine the pathogens causing early and late onset neonatal sepsis and their antimicrobial susceptibility
3. To determine sepsis related deaths (within 5 days of a positive culture)

METHODOLOGY

This is a retrospective cross sectional analysis of an existing database. Neonates admitted to the Charlotte Maxeke Johannesburg Hospital (CMJAH) neonatal unit between 01 January 2015 and 31 December 2016 will be included. This is a tertiary hospital with a specialised neonatal unit, which include neonatal intensive care unit (NICU) and neonatal ward.

Database

Demographic and clinical information is collected on discharge for each neonate admitted to the CMJAH neonatal unit. The data is entered into a database using Research Electronic Data Capture (REDCAP) hosted by the University of the Witwatersrand [17]. Data is verified at several points during the collection process.

Neonates with positive bacterial cultures will be obtained from the National Health Laboratory Service (NHLS) using trakcare. Relevant clinical and demographic information will be obtained from the CMJAH REDCAP database (see the data collection sheet attached). Details regarding the pathogen and antimicrobial sensitivity patterns will be obtained from NHLS.

Inclusion criteria

- Neonates with positive bacterial blood cultures admitted within 72 hours of life Exclusion criteria
- Neonates whose records are unobtainable.

Statistical Analysis:

The categorical variables to be analysed are frequency, and percentages while the continuous variable to be analysed are mean, standard deviation and median. The expertise of a stastician will be utilised during the analysis of data. The definition of sepsis in this study is culture proven sepsis and we regarded the following organisms as contaminants; *Corynebacterium* spp., *Bacillus species* and *Micrococcus spp*. while coagulase- negative *Staphylococcus (CoNS)* and *Viridans Streptococci* were considered significant. A data capture sheet with specific variables of interests will be used. It will not contain any names, hospital number or date of birth to ensure that the information cannot be traced back to the participant (neonates). Each neonate will be

assigned a study number decided by the researchers. The study will look at neonates admitted between 01 January 2015 and 31 December 2016. It is a retrospective study and the endpoint will be positive blood culture results with bacterial isolates and antibiotic susceptibility. The other outcome of interest in this study will also include sepsis related death (SRD), if the death occurs within five days of positive blood culture.

ETHICS

The research protocol will be submitted to the Human Research Ethics Committee of e the University of Witwatersrand, Ethic committee for approval before any data collection. This is to ensure that there are no violations of patient' rights and the study is conducted in an ethical manner. The information obtained from the study will be used to benefit neonates admitted to the unit in the future and form part of database that can be used for future research that will improve how we provide health care service to our patients.

TIMING

	Ma	Apr	Ma	Jun	July	Aug	Sep	Oct	Nov	Dec	Jan
Protocol development											
Ethics/PG Committee											
Data collection											
Data analysis											
Write up											
Submission											

FUNDING: The costs of the study are anticipated to be minimal. A budget of R 500 is proposed for stationery and printing which will be borne by the researcher. References

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HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170407

NAME: (Principal Investigator)	Dr Moses Matlhadisa
DEPARTMENT:	Paediatrics Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Epidemiology of Bacterial Bloodstream Infections in Neonates at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	05/05/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	Prof Ballot and Dr Vindana Chibabai Professor P. Cleaton-Jon ..s, Chairperson, HREC (Medical)
DATE OF APPROVAL:	07/06/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

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To be completed in duplicate and ONE COPY returned to the Research Office Secretary 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. I agree to submit a yearly progress report. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in April and will therefore be due in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

_____ _____ Principal

Investigator Signature Date

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