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Original Research Article

A study on characterisation of antimicrobial resistance and antibiotic susceptibility pattern in late preterm and term neonates in a tertiary hospital, Imphal

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ABSTRACT

Background: Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first four weeks of life. It may further be divided into two main classes: early onset sepsis, which presents within the first 72 hours of birth and late onset sepsis, which usually presents after 72 hours after birth. The pattern of organisms causing neonatal sepsis has been constantly changing and the indiscriminate use of antibiotics had resulted in the emergence of multidrug resistant and virulent organisms. This study aimed to evaluate neonatal infections and the antibiotic susceptibility patterns.
Methods: An institution based cross sectional study in a NICU of a tertiary care hospital. Cases enrolled were both intra and extramural who got admitted during the study period. Informed consent was obtained from the parents/guardians.
Results: There were a total of 138 participants in the study. All of them tested positive for sepsis screen. Neonatal sepsis was more common in late pre-terms (57.2%) than terms (42.8%). Gram negative bacteria were the main causative agents with *E. coli* (9.4%) being the most common isolate followed by *Acinetobacter baumanii* (8%) and *Klebsiella* (8%). The most common gram-positive organism isolated was budding yeast cells (*Candida* spp.). Among gram positive bacteria the most common isolates were methicillin-resistant *Staphylococcus aureus* (MRSA) (5.8%) and coagulase-negative *Staphylococci* (CONS) (3.6%). Tigecycline and colistin were most sensitive antibiotics showing the least resistance to all organisms.
Conclusions: The antibiotic sensitivity patterns have changed and the morbidity load is higher in pre-terms compared to terms.

Keywords: Preterms, Sepsis, Antibiotic, MRSA, CONS

INTRODUCTION

Sepsis is one of the leading causes of neonatal mortality accounting for 18.6% of neonatal deaths and continues to be a formidable challenge for pediatricians worldwide. According to the national neonatal perinatal database 2002-2003, the incidence of neonatal sepsis was 30 per 1000 live births.[1] World health organization has estimated that 1.6 million deaths occur globally due to sepsis and 40% of those occur in developing countries. In India, the incidence of blood culture proven sepsis was reported as 8.5 per 1,000 live births for the year 2002-2003 by the national neonatal perinatal database (NNPD report 2002-03).[2]

Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first four weeks of life.[3] It may further be divided into two main classes depending on the onset of

symptoms namely, early onset sepsis, which presents within the first 72 hours of birth and late onset sepsis, which usually presents after 72 hours after birth.[4] Early onset sepsis is acquired during fetal life, at the time of birth or at the nursery. The earliest signs of sepsis are often subtle and non-specific like hypothermia or fever, lethargy or poor cry, decreased sucking, increased perfusion time, hypotonia and bradycardia.

The pattern of organisms causing neonatal sepsis has been constantly changing and the indiscriminate use of antibiotics has resulted in the emergence of multidrug resistant and virulent organisms. Here lies the importance of microbiological investigation and determination of antibiotic susceptibility pattern of the isolate. As high as 47.5%-64% incidence of bacteremia has been reported in neonates previously with gram-negative organisms such as *Klebsiella*.[5] In most developing countries, gram-negative bacteria like *Klebsiella* remain the major source of infection. However, in the developed countries, gram-positive organisms have been implicated as the most common cause.[6] For effective management of neonatal septicemia, study of their antibiotic sensitivity plays significant role. The organisms responsible for neonatal sepsis vary across geographical boundaries and with the time of onset of illness.

Early treatment with appropriate use of antibiotics would reduce the risk of severe morbidity and mortality due to infections, and also the emergence of multi-drug resistant organisms. For the success of early empiric treatment, periodic studies to assess any changing trends in the infecting organisms and their antimicrobial susceptibility is important.[7]

Neonatal sepsis is also, very much a prevalent entity in Manipur accounting for significant neonatal mortality and morbidity. Although, a few studies have been conducted in the past so as to establish the causative factors, there has been a lack of in-depth analysis about the changing trends in the causative organisms, as well as the emergence of new antibiotic susceptibility and resistance patterns. Keeping all these in mind, this study was taken up among all the late preterm and term newborns admitted with clinical features of sepsis in pediatric ward RIMS, Imphal over the period of the two years.

Aims and objects

The aim and objectives were to determine the common organisms causing sepsis in late pre-term and term neonates in the Unit and ascertain their susceptibility and resistance to various antibiotics.

METHODS

Study design

An institutional based cross-sectional study design used for this study.

Study setting

The study was conducted in the department of paediatrics and microbiology, regional institute of medical sciences, Imphal, Manipur, India.

Duration of study

The study was conducted over a period of 24 months (September 2019 to August 2021).

Study population

The study population consisted of all late preterm and term neonates admitted for sepsis in paediatrics department, RIMS, Imphal, Manipur.

Inclusion criteria

Late preterm and term neonates with clinical suspicion of sepsis and late preterm and term neonates with a positive sepsis screen were included in the study.

Exclusion criteria

Patients with birth weight <1.5 kg, gestational age <34 weeks, parents not willing to give consent were excluded from the study.

Sample size

All neonates fulfilling our inclusion criteria who got treatment in the unit during the study period.

Study variables

Independent variables: Neonatal birth weight (kg), sepsis screen status (positive or negative), sex of the neonate, timing of onset of disease, period of gestation.

Outcome variables: Common organisms involved in late preterm and term neonatal sepsis and antibiotic sensitivity and resistance patterns.

Data collection

Informed consent was obtained from the parents/guardian regarding inclusion in the study. After obtaining the informed consent from the parents/guardian regarding inclusion of the neonate in the study, assessment was done. Blood samples were obtained using strict aseptic procedure using sterile gloves and all other necessary requirements.

Technique for drawing blood culture

Preparation of the site

The site of venipuncture was selected, examination gloves were put, after strict hand washing, the area was

cleansed with 70% isopropyl alcohol or ethyl alcohol to remove surface dirt and oils. The venipuncture site was scrubbed gently, but firmly with the cotton beginning in the centre and continuing in an outward direction, the site was allowed to dry, the site was swabbed in concentric circles of povidone (1%)/ chlorhexidine (2%), in a similar manner given earlier beginning in the center and continuing in outward direction, the area was cleansed with 70% isopropyl alcohol or ethyl alcohol again as mentioned before. the site was allowed to dry, after the 3rd swab, the site was allowed to dry for at least 60 seconds, during this period, the lids of blood culture bottles were prepared with iodine and/or alcohol with sterile gloves, dried iodine at venipuncture site was rubbed off with alcohol, 1 ml of blood was drawn and placed in each bottle (these bottles constituted of 1 blood culture set) and the bottles were inoculated after changing the needles

For infants up to 1 year of age recommended blood to be collected is 1-1.5 ml (ICMR guidelines)

Lumbar puncture

Indications were-all neonates with clinical features suggestive of meningitis and lumbar puncture must be performed to exclude meningitis since the presence of meningitis alters the length of antibiotic treatment as well as prognosis.

Urine culture and microscopy

Indications were-late onset sepsis especially presenting with unexplained fever, patients at risk of fungal sepsis, poor weight gain and unexplained cholestasis.

UTI is diagnosed in the presence of one of the following-5 WBC/HPF, 10^4 organisms/mL in the urine obtained by catheterisation and any organism found in urine obtained by supra pubic aspiration.

Endotracheal tube tip culture and sensitivity

For all neonates who were intubated and mechanically ventilated.

Umblical venous catheter tip culture and sensitivity

For neonates in whom UVC was inserted.

Study tools

Pre-tested performa for: History and clinical examination and investigations.

Instruments used were 2 ml sterile syringes, blood culture bottles (BacT/ALERT), 70% isopropyl alcohol or ethyl alcohol, povidone iodine (1%)/ chlorhexidine (2%), sterile gauze/ swabs and urine vials.

Working definitions

Neonate: Neonates were less than 28 days old new born.

Term: Period of gestation of 37 weeks to 42 weeks.

Late preterm: Period of gestation of $34^{0/7}$ weeks to $36^{6/7}$days.

Culture positive sepsis: Isolation of a recognised pathogen from blood, cerebrospinal fluid, or other body fluids in neonates suspected to have sepsis on the basis of clinical features or maternal or prenatal risk factors, along with treatment involving appropriate type and duration of antibiotic therapy. Case of sepsis with positive culture for CONS were labelled only if the clinical course suggestive of sepsis and appropriate antibiotic therapy was given.

Culture negative sepsis: Clinical course suggestive if sepsis or positive sepsis screen, but no pathogen isolated or blood culture not done.

Total sepsis: Number of neonates with culture positive sepsis or culture negative sepsis.

Early onset sepsis: Occurrence of sepsis at or before 72 hours of life.

Late onset sepsis: Occurrence of sepsis after 72 hours of life.

Meningitis: Positive cerebrospinal fluid culture, gram-staining or neutrophilic leucocytosis, with or without low sugar and high protein content.

Positive sepsis screen

Positive sepsis screen included-TLC<5000/mm^3 or >18000/mm^3, CRP-positive (NR 0-6 mg/dl), micros ESR>15 mm/1st hour, ANC<1800/mm^3 and IT ratio:>0.2.

Statistical analysis

IBM SPSS software version-21 for Windows was used for statistical analysis. Data collected was checked for completeness and data was entered in SPSS version-21 for windows. Descriptive statistics like mean, standard deviation and percentages were used. The data obtained was tabulated and was analysed for their association by applying the Fisher's exact test, Chi-square test, and calculation of p value. $P<0.05$ was considered significant.

Ethical approval

Ethical clearance was obtained from research ethic's board no. A/206/REB-Comm (SP)/RIMS/2015/575/53/2019, regional institute of medical sciences, Imphal.

RESULTS

There was a total of 138 participants in the study. The minimum age was 1 day while the maximum age was 42 days with a mean and standard deviation of 5.47±7.54 days. The mean birth weight and standard deviation of the participants was 2.35±0.53 kg with a minimum birth weight of 1.5 kg and a maximum birth weight of 3.4 kg. All of them tested positive for the sepsis screen. More than half of the participants (60.9%) were males while females comprised of only 39.1% of which late pre-terms comprised of 57.2% while 42.8% were terms. More than half (53.6%) of the participants had birth weight of >2.5 kg while 46.4% were low birth weight. 26.1% of the participants were admitted in neonatal intensive care unit.

Table 1: Demographic data of the cases.

Gender		Gestation		Birth weight (Kg)		NICU		Culture		Onset	
M	F	Preterm	Term	≤2.5	>2.5	Yes	No	+ve	-ve	EOS	LOS
54	84	79	59	64	74	36	102	38	100	111	27

Majority of the patients presented with respiratory distress 65 (47.1%) followed by low birth weight 21 (15.2%), jaundice, seizures, birth asphyxia and decreased feeding. The 81.1% of them had early onset septicemia while 18.9% had late onset septicemia. The 38 (27.5%) of those samples showed the presence of pathogens while 100 (72.5%) were sterile. Only 0.7% of the samples of cerebrospinal fluid showed the presence of growth of pathogens. The 15.2% of the samples from endotracheal tube tip showed the presence of pathogens. Likewise, 0.7% of the samples from the umbilical venous catheter showed growth of pathogens. Of the bacteria that were isolated from the samples sent for culture, gram-negatives constitute 75.86% while gram-positives comprised 24.14%. *E. coli* (19.1%) was the most commonly isolated gram-negative bacteria while MRSA (11.7%) was the most common gram-positive bacteria. *Candida* species (16.1%) were the most common fungal isolate.

Table 2: Distribution of pathogens isolated from the specimens.

Organisms		N (%)
Gram-positive	Coagulase negative *Staphylococcus*	5 (7.3)
	MRSA	8 (11.7)
	Staphylococcus haemolyticus	1(1.4)
Gram-negative	*Acinetobacter baumanii*	11 (16.1)
	Burkholderia cepacia	1 (1.4)
	Escherichia coli	13 (19.1)
	Enterobacter cloaca	2 (2.9)
	Klebsiella pneumoniae	11 (16.1)
	Pseudomonas aeruginosa	5 (7.3)
Other organisms	Gram-positive budding yeast cells (*Candida* species)	11 (16.1)

Amikacin (36.8%) was the most sensitive aminoglycoside followed by gentamicin (26.3%). Meropenem was the most sensitive beta-lactam antibiotic while tigecycline (57.8%) was the most sensitive tetracycline antibiotic. The 19.2 % of the patients were sensitive towards ceftazidime among the cephalosporin group of antibiotics. Other antibiotics which were shown to be sensitive were linezolid, colistin, teicoplanin, novobiocin, mupirocin, piperacillin, vancomycin, dicloxacillin, cotrimoxazole and metronidazole. Among them colistin (49.1%) was found to be the most sensitive.

Among the anti-fungals, the most sensitive was fluconazole (12.2%).

Resistance to aminoglycosides was seen almost equally among the different aminoglycosides. Resistance to amikacin, gentamicin and netilmicin was 28%, 26% and 24.5% respectively. Resistance is more observed in imipenem (28%) than meropenem (5.2%) amongst the beta-lactam antibiotics. Quinolones antibiotic resistance was more common with ciprofloxacin (36.8%). The 1.7% of the patients showed resistance to both tigecycline and minocycline. Azithromycin and erythromycin resistance was seen more among the macrolides with 22.8% and 19.2% respectively. Cephalosporins such as cefepime and ceftazidime resistance was seen in 22.8% and 17.5% respectively. Amongst other antibiotics such as tiecoplanin, novobiocin, mupirocin, piperacillin, vancomycin, aztreonam, trimethoprim and cotrimoxazole, resistance was seen with mupirocin (36.8%) and cotrimoxazole (29.8%).

Resistance to aminoglycosides was seen almost equally among the different aminoglycosides. Resistance stood at 28%, 26% and 24.5% respectively for amikacin, gentamicin and netlimicin. Of the tetracyclines. Ampicillin resistance (35%) was more commonly seen among the penicillin group of antibiotics.

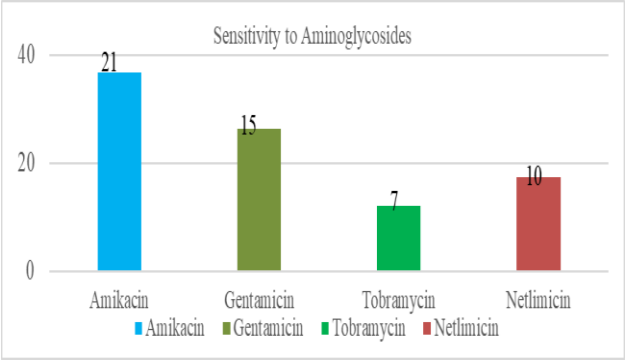

Figure 1: Distribution of bacterial isolates according to sensitivity to aminoglycosides.

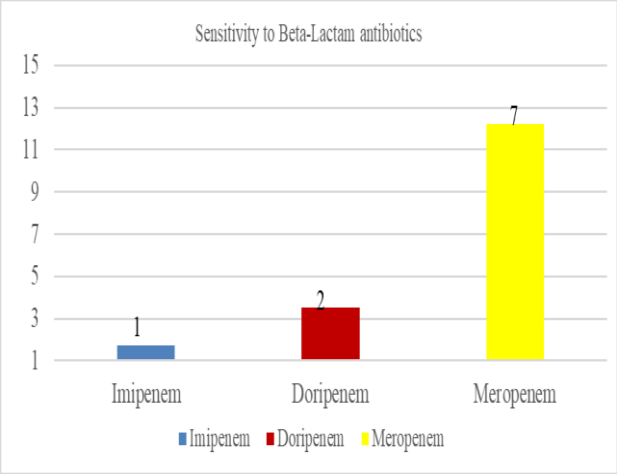

Figure 2: Distribution of participants according to sensitivity to beta-lactam.

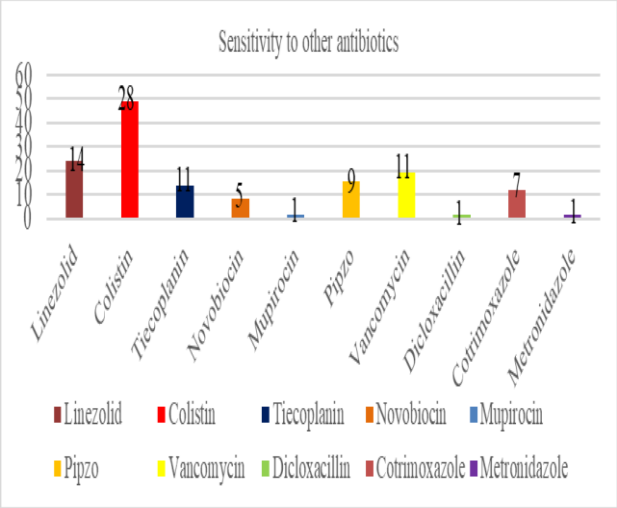

Figure 3: Distribution of participants according to sensitivity to other antibiotic.

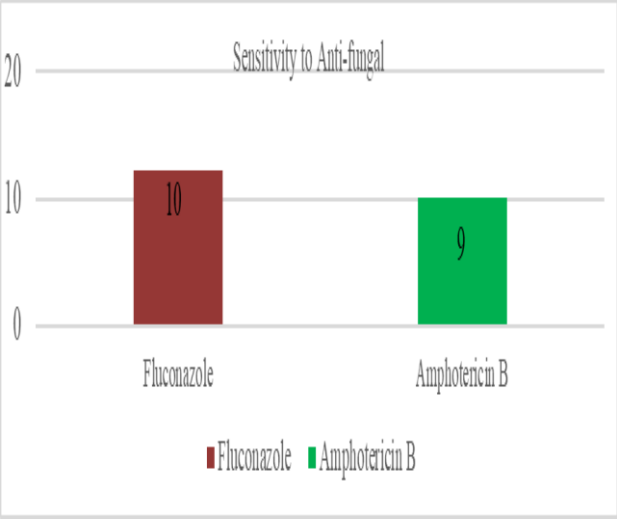

Figure 4: Distribution of fungal isolates according to sensitivity to anti-fungals.

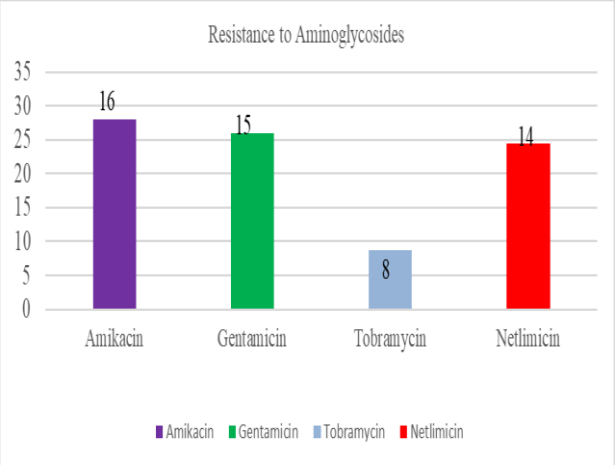

Figure 5: Distribution of pathogens according to resistance to aminoglycosides.

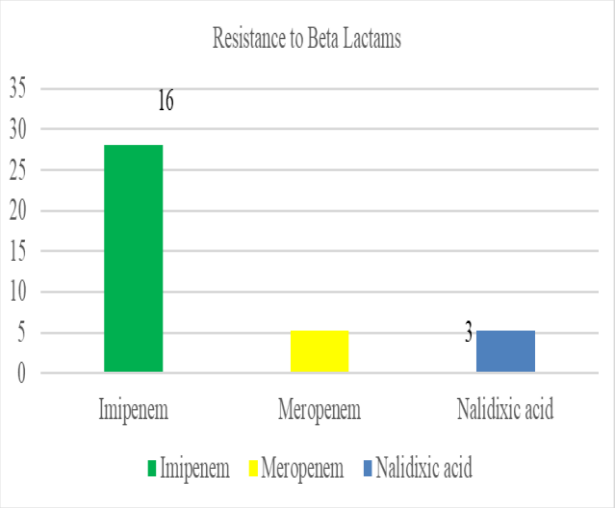

Figure 6: Distribution of pathogens according to resistance to beta-lactams.

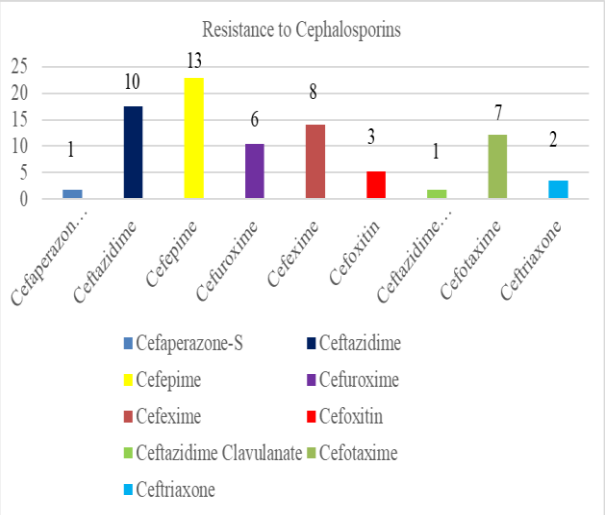

Figure 7: Distribution of pathogens according to resistance to cephalosporins.

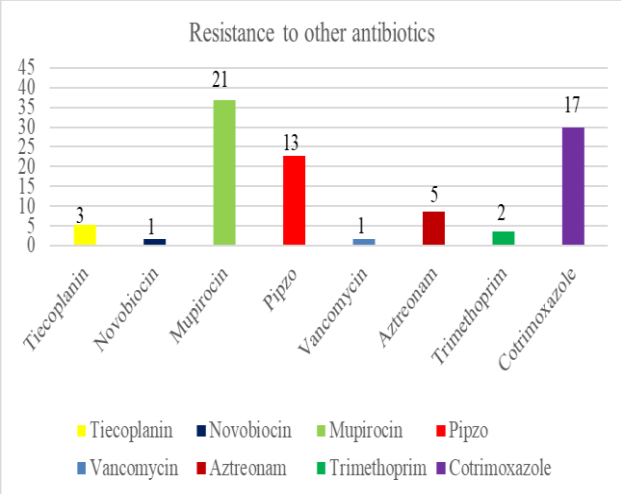

Figure 8: Distribution of pathogens according to resistance to other antibiotics.

DISCUSSION

Neonates are immunocompromised individuals who are prone to infections with significant morbidity and mortality.[19] The clinical manifestations range from subclinical infections to severe systemic infections. The infections can rapidly deteriorate and prompt identification and treatment are needed. As such, it is imperative to determine the common organisms involved in sepsis in late pre-term and term neonates. This study was able to recruit 138 patients with a mean age of 5.47±7.54 years and the average weight of 2.35±0.53 kg. All 138 tested positive in the sepsis screening. The most common clinical presentation that was observed in these patients was respiratory distress. This is an expected finding as acute respiratory distress is a devastating complication of severe sepsis.[20] Sepsis and ARDS have similar underlying mechanisms, characterized by inflammation and endothelial dysfunction. In addition, severe sepsis is the most common aetiology of ARDS, and patients with sepsis-induced ARDS have higher case fatality rates than patients with other risk factors of ARDS.[21] Neonatal sepsis is caused by gram-positive and gram-negative bacteria and *Candida*.[22] The diversity of organisms causing sepsis varies from one region to another and changes over time even in the same place.[23] This is attributed to the changing pattern of antibiotic use and changes in lifestyle.[24] The knowledge of bacteriological profile and its antibiotic sensitivity patterns is of immense help in saving lives of neonates with septicaemia.[25] The prevalence of bacterial profile of blood culture and their susceptibility patterns in an area, provide guidance to start empirical treatment which is the cornerstone in the management of sepsis.[26] In this study, 138 patients had a positive sepsis screen. Out of these, culture and sensitivity testing were sent for all patients. Both gram-positive and gram-negative organisms were isolated from these cultures. Gram positive budding yeast cells (*Candida* spp) were the most common gram-positive organism that was isolated (8%). On the other hand, *Escherichia coli* was the most commonly isolated gram-negative bacteria (9.4%). Other gram-negative organisms isolated included. *Acinetobacter baumanii, Klebsiella pneumonia, Pseudomonas aureginosa*, etc.

The most sensitive antibiotic in this study was found to be tigecycline (23.9%) and colistin (20.3%). Tigecycline is known to exhibit anti-bacterial activity against a wide spectrum of aerobic and anaerobic bacteria. In the case of colistin, a study conducted by Jasani et al suggested that intravenous colistin appeared to be safe and efficacious in critically sick preterm and term neonates with sepsis.[27]

The aminoglycosides are a critical component of the current antibacterial arsenal.[28] The broad-spectrum nature of these antibiotics and their rapid bactericidal activity favours them as an important class of antibiotic group. The aminoglycoside which produces the highest susceptibility in this study was amikacin. This is in accordance with a study conducted by Thapa et al which found that amikacin was the most effective drug for both gram-positive and gram-negative isolates.[29] Aminoglycosides are particularly active against aerobic, gram-negative bacteria and act synergistically against certain gram-positive organisms.[30] This study also found that gram-negative organisms are more likely to respond to aminoglycosides than gram positive organisms. Cephalosporins are anti-microbials grouped into five generations based on their spectrum of coverage against gram-positive and gram-negative bacteria and their temporal discovery. They are effective against gram-negative bacteria, but show some reduced activity against gram-positive bacteria.[31] The same scenario is seen in this study where cephalosporins were found to be more effective against gram-negative organisms than gram-positive organisms. On the other hand, fungal isolates are more likely to respond to fluconazole than amphotericin B.

The worldwide spread of antimicrobial resistance represents a major challenge with nearly half of the pathogens that cause severe neonatal bacterial infections reported to be resistant to the first-line (ampicillin or penicillin, and gentamicin) and second-line (third-generation cephalosporins) WHO-recommended treatments.[32] The bacterial resistance to antibiotics results mainly from the selective pressure exerted by the use and overuse of antibiotics.[33] In this study, resistance was seen in almost all groups of antibiotics. Resistance was most commonly seen in ciprofloxacin (15.2%) and mupirocin (15.2%). It has been established that the β-lactam antibiotic must first diffuse through the bacterial cell wall. Gram-negative organisms have an additional lipopolysaccharide layer that decreases antibiotic penetration.

Therefore, gram-positive bacteria are usually more susceptible to the action of β-lactams than gram-negative bacteria. The findings in this study also reinforces the validity of this statement as it was observed that gram-

negative organisms were more likely to be resistant to beta lactams than gram-positive organisms. In general, macrolide antibiotics are active mainly against gram-positive bacteria and have only limited activity against gram-negative bacteria.[34] However, macrolide resistance in gram-positive cocci has increased dramatically all over the world.[35] This study also found that gram-positive microorganisms were more likely to be resistant to macrolides than gram-negative antibiotics.

The limitation of this study was that, certain extramural patients reported to our centre after receiving empirical antibiotics elsewhere while the ideal sampling should be done before it. Emphasis should also be laid on the use of sterile techniques while inserting devices, hand hygiene and use of gowns and gloves to prevent nosocomial infections and better patient response and clinical outcome.

CONCLUSION

A hospital based cross-sectional study was conducted in 138 neonates who presented with clinical signs and symptoms of septicemia in a tertiary hospital in Imphal from September 2019 to August 2021 with an aim to study the common organisms involved in causing neonatal septicemia in late preterm and term neonates. The majority of organisms isolated belonged to gram-negative group with 65.2% while gram-positive comprised of 34.5%. Among gram negative *E. coli* was the most common organism isolated followed by *Acinetobaceter baumanii*, *Klebsiella pneumonia* and *Pseudomonas aureginosa*. Next most common isolate were gram positive budding yeast cells. Among gram positive bacteria, MRSA comprised the majority followed by CONS. Tigecycline was the most sensitive antibiotic followed by colistin. Gram-negative organisms were more sensitive towards aminoglycosides and cephalosporins with amikacin being the most sensitive followed by gentamicin while they are more likely to be resistant to penicillins. Gram positive organisms on the other hand are more likely to be resistant to macrolides. Gram positive budding yeast cells were sensitive to antifungals like fluconazole and amphotericin B. Based on this study, we will be able to identify the prevalent organisms in our setting and our empirical treatment can be pointed towards the antibiotics and antifungals they are more susceptible to.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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