Bacteriological profile and antibiotics sensitivity patterns among neonates admitted at Birat Medical College Teaching Hospital

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ABSTRACT

Background: Neonatal sepsis still remains serious and potentially life-threatening events with a mortality rate of up to 50%. The current practice of starting empirical antibiotic therapy in all neonates showing infection-like symptoms results in their exposure to adverse drug effects, nosocomial complications, and in the emergence of resistant strains. The antibiotic sensitivity pattern of organisms is changing very rapidly over a short period which is varying from country to country, one place to another, and one institute to another. Therefore, periodic evaluation of sensitivity patterns is essential for rational and appropriate use of antibiotics. **Aims and Objectives:** This study aims to see bacteriological profile and their antibiotics sensitivity among the sepsis suspected neonates at the neonatal intensive care unit of Birat Medical College Teaching Hospital (BMCTH). **Materials and Methods:** It was a cross-sectional descriptive study from July 21, 2021, to December 21, 2021. Sample size of 138 was included in the study. Neonates were selected by non-probability consecutive sampling techniques. Neonatal sepsis suspected neonates and plan to treat with injectable antibiotics by the treating pediatrician were included in the study. All patients included were started on empirical antibiotics after drawing samples for blood cultures and CRP along with other investigations. Bacteriological profile and their sensitivity to different antibiotics were collected from blood culture reports. Data collection was done using a specifically designed questionnaire. The descriptive and inferential statistics were used for data analysis. The test of significance was done by the Chi-square test. P<0.05 was considered statistically significant. **Results:** Among the 46 blood culture-proven sepsis, the most common organism isolated was *Staphylococcus aureus* which was 33 (71.7%). Among the isolated *S. aureus*, 100% were sensitive to colistin sulfate and injectable linezolid, 93.1% sensitive to injectable meropenem, 85.7% sensitive to injectable piperacillin and tazobactam combination, 83.3% sensitive to injectable vancomycin, and 85.7% sensitive to injectable amikacin but only 40.7% to injectable cefotaxime. Isolated *Acinetobacter* species were found 100% sensitive to colistin sulfate and meropenem, and 80% sensitive to cefotaxime and amikacin but only 66.7% sensitive to injectable piperacillin and tazobactam combination. Only one neonate had *Klebsiella* isolated in blood culture which was 100% resistant to injectable cefotaxime but was sensitive 100% to Meropenem, piperacillin-tazobactam, and amikacin. Isolated *Enterococcus* species were 100% sensitive to piperacillin-tazobactam combination, meropenem, and imipenem but only 66.7% sensitive to injectable cefotaxime. **Conclusion:** Gram-positive isolates were the predominant pathogens among enrolled neonatal sepsis suspected neonates at Birat medical college teaching hospital (BMCTH). Based on our findings, a combination of cefotaxime and amikacin can be used as first-line therapy. However, cefotaxime only had moderate sensitivity, so change to piperacillin-tazobactam and vancomycin or linezolid as second-line therapy can be considered early in case of no improvement or deterioration, or combination of vancomycin and meropenem as third line would be the appropriate empirical

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therapy at BMCTH. However, the use of the broad-spectrum antibiotics as empirical therapy should be evaluated in the long run and should be used cautiously and modified to narrow spectrum antibiotics, as guided by the culture and susceptibility report at the earliest possible.

Key words: Blood culture; Neonatal sepsis; Neonates

INTRODUCTION

During the past decades, advances in neonatal intensive care have led to an impressive decrease of neonatal mortality and morbidity. However, infectious episodes in the early postnatal period still remain serious and potentially life-threatening events with a mortality rate of up to 50% in very premature infants. The signs and symptoms of neonatal sepsis are clinically indistinguishable from various non-infectious conditions such as respiratory distress or maladaptation. The current practice of starting empirical antibiotic therapy in all neonates showing infection-like symptoms results in their exposure to adverse drug effects, nosocomial complications, and in the emergence of resistant strains.[1] The antibiotic sensitivity pattern of organisms is changing very rapidly over a short period which is varying from country to country, one place to another, and one institute to another. It is particularly true for the developing countries like Nepal where antibiotics are prescribed irrationally not only by the medical practitioners but the antibiotics are also purchased directly from the chemists like medicine shopkeepers without prescription. It has been advised that clinicians should be aware of the rising resistance of bacteria to commonly prescribed antibiotics as well as the profile of antibiotic resistance. Therefore, periodic evaluation of sensitivity patterns is essential for rational and appropriate use of antibiotics.[2]

Hence, we aimed to prepare a bacteriological profile list of the common organisms causing sepsis among neonates and to develop an institutional bacteriological profile and their sensitivity pattern at neonatal intensive care unit of Birat Medical College Teaching Hospital (BMCTH). This will help us for rational and appropriate use of antibiotics and will cut down the treatment cost, lessen the adverse effects due to drugs, decrease duration of hospital stay, prevent emergence of antibiotics resistant, and will decrease the overall neonatal morbidity and mortality.

Aims and objectives
This study aims to see bacteriological profile and their antibiotics sensitivity among the sepsis suspected neonates at the neonatal intensive care unit of BMCTH.

MATERIALS AND METHODS

It was a cross-sectional descriptive study from July 21, 2021, to December 21, 2021. Suspected neonatal sepsis was considered if neonate had clinic pathological features of perinatal risk factors, that is, maternal pyrexia (within 1 week prenatal and/or 48 h postnatal), prolonged rupture of membranes (18 h), foul smelling vaginal discharge, or/and maternal urinary tract infection diagnosed in the past month. Neonates having unexplained hypothermia/hyperthermia, lethargy, irritability, poor feeding or milk intolerance, and tachypnea, cardiovascular dysfunction such as persistent tachycardia (>160 beat/min) or bradycardia (<100 beats/min), hypotonia, circumoral pallor, cyanosis, and poor peripheral circulation, babies who had suffered birth asphyxia, very low birth weight <1500 g, and extremely premature <32 weeks gestation. About 138 sample sizes were calculated using expected prevalence 10%, desired precision 5%, and confidence level 95%. After taking informed and written consent from parents and permission from the Institutional Review Committee, neonates brought to the neonatal unit were selected by purposive sampling technique. Neonatal sepsis suspected neonates were included in the study. Neonates who already had taken antibiotics before admission, whose blood culture and sensitivity could not be sent before giving antibiotics, and parents unwilling to give written consent were excluded from the study. All patients included were started on empirical antibiotics after drawing samples for blood cultures and CRP along with other investigations advised by the treating physician and sent to the laboratory. Strict aseptic measures were taken while taking blood for investigations. For CRP, blood was collected in plain vial without any anticoagulants and the tests were performed by HumaTex CRP latex agglutination slide test. A second sample for determination of CRP was drawn 72 h after the first one. For blood culture, 1 ml of blood were drawn. Blood culture bottles were checked for expiry date printed on each bottle. A 1ml of blood were inoculated in the blood culture bottles containing media, that is, blood agar or MacConkey agar media for aerobic culture. Blood culture bottles were clearly labeled with the name of the patient and date and time of collection of blood before sending to laboratory. Blood culture and sensitivity were performed by BD BACTEC.

CRP was read as negative when the level was <6 mg/dl and positive when the level was equal to more than 6 mg/dl. Blood culture was followed for growth up to 7 days. Data collection was done using a specifically designed questionnaire. All the data were entered into Excel sheets and transferred to

SPSS version 20. The descriptive and inferential statistics were used for data analysis.

RESULTS

This study included 138 neonates who met the inclusion criteria. Among the study population, 98 (71%) were male and 40 (29%) were female (Figure 1).

Similarly, Figure 2 shows distribution of enrolled neonates according to birth weight. Among them, 32 (23.2%) were low birth weight babies, that is, weight <2500 g, 85 (61.6%) were babies of normal birth weight, that is, weight 2500–3900 grams, 7 (5.1%) were large babies, that is, birth weight >3900 grams, 13 (9.4%) were babies of very low birth weight, that is, birth weight of <1500 grams, and 1 (0.7%) was of incredible weight, that is, birth weight <1000 grams (Figure 2).

Among the study population, 125 (90.5%) had early-onset neonatal sepsis among which pneumonia and birth asphyxia was the most common cause. While 13 (9.5%) had late-onset neonatal sepsis among which exaggerated neonatal jaundice, AGE and fever were significantly higher in late-onset sepsis rather than the early-onset sepsis (Table 1).

Among the enrolled neonates suspected of sepsis, 46 (33.33%) had blood culture-proven sepsis while 87 (63.04%) had blood culture which were negative for any growth and were sterile. Furthermore, 5 (3.62%) of the patient had contaminated blood culture and were excluded from final analysis (Table 2).

Among the 46 blood culture-proven sepsis, the most common organism isolated was *Staphylococcus aureus* which was 33 (71.7%), *Acinetobacter* species was isolated in 7 (15.21%), *Enterococcus* species in 4 (8.6%), *Klebsiella* species in one patient, and *Micrococcus* species in one patient. Among the isolated *S. aureus*, blood culture report revealed 100% sensitive to colistin sulfate and injectable linezolid, 93.1% sensitive to injectable meropenem, 85.7% sensitive to injectable piperacillin and tazobactam combination, 83.3% sensitive to injectable vancomycin, and 85.7% sensitive to injectable amikacin but only 40.7% to injectable cefotaxime. Isolated *Acinetobacter* species were found 100% sensitive to colistin sulfate and meropenem, 80% sensitive to cefotaxime and amikacin but only 66.7% sensitive to injectable piperacillin and tazobactam combination. Only one neonate had *Klebsiella* isolated in blood culture which was 100% resistant to injectable cefotaxime but was sensitive 100% to meropenem, piperacillin-tazobactam, and amikacin. Isolated *Enterococcus* species were 100% sensitive to piperacillin-tazobactam combination, meropenem, and imipenem but only 66.7% sensitive to injectable cefotaxime (Table 3).
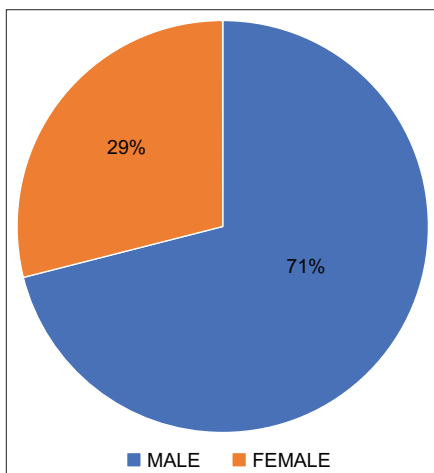
DISCUSSION

Neonatal sepsis is considered the leading cause of infant mortality and morbidity in the neonatal intensive care unit.[1] The antibiotic sensitivity pattern of organisms is changing very rapidly over a short period which is varying from country to country, one place to another, and one institute to another. It is particularly true for the developing countries like Nepal where antibiotics are prescribed irrationally not only by the medical practitioners but the antibiotics are also purchased directly from the chemists like medicine shopkeepers without prescription. It has been advised that clinicians should be aware of the rising resistance of bacteria to commonly prescribed antibiotics as well as the profile of antibiotic resistance. Therefore, periodic evaluation of sensitivity patterns is essential for rational and appropriate use of antibiotics.[2]

Figure 1: Distribution of enrolled neonates according to gender
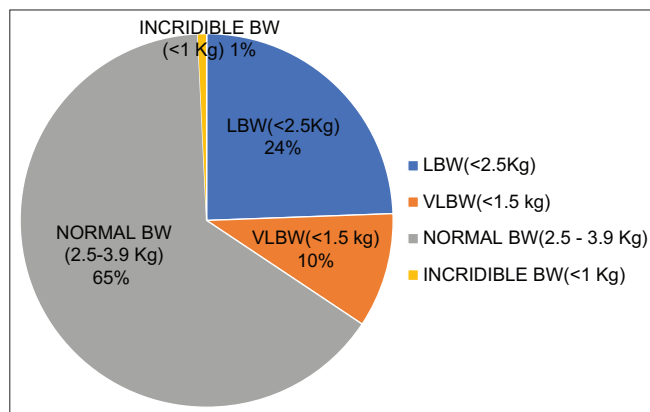
Figure 2: Pie chart showing distribution of enrolled neonates according to birth weight

Table 1: Risk factors for sepsis of neonates

	Early-onset Sepsis, n=125	Late-onset Sepsis, n=13	Total (%)	P value*
Birth asphyxia with prematurity with LBW with respiratory distress	6	0	6 (4.3)	0.546
Congenital pneumonia	15	3	18 (13.0)	0.377
Birth asphyxia	21	0	21 (15.2)	0.217
Prematurity with VLBW	12	0	12 (8.7)	0.604
Prematurity with LBW	19	1	20 (14.5)	0.692
Birth asphyxia with meconium aspiration syndrome	16	0	16 (11.6)	0.363
Respiratory distress	13	2	15 (10.9)	0.634
Exaggerated neonatal jaundice	1	3	4 (2.9)	0.003
PROM and PV leaking	15	0	15 (10.9)	0.360
Age	0	2	2 (1.4)	0.008
Neonatal pustulosis	1	0	1 (0.7)	0.906
Low birth weight with IUGR	1	0	1 (0.7)	0.906
Fever	2	2	4 (2.9)	0.044
Maternal fever or risk of infection in the week of delivery	3	0	3 (2.2)	0.741

*Fisher's exact Chi-square test

Table 2: Blood culture reports of enrolled neonates

Blood culture	Number of patient	Total
Negative	87	87 (63.04)
Positive	46	46 (33.33)
Contaminated**	5	5 (3.62)

Hence, we aimed to prepare a bacteriological profile list of the common organisms causing sepsis among neonates and to develop an institutional bacteriological profile and their sensitivity pattern at neonatal intensive care unit of BMCTH. This will help us for rational and appropriate use of antibiotics and will cut down the treatment cost, lessen the adverse effects due to drugs, decrease duration of hospital stay, prevent emergence of antibiotics resistant, and will decrease the overall neonatal morbidity and mortality.

No previous such studies were performed at the Pediatrics Department of BMCTH. The first and pioneer such study at our neonatal intensive care unit showed culture positivity of 46 (33.33%) among enrolled 138 neonates with suspicion of sepsis. Similar study, done by Pokharel et al., at Patan Hospital in Nepal, showed culture positivity of neonatal sepsis to be 20.7% but it was a retrospective study.[3] In contrast, studies conducted at KIST Medical College and Manipal College of Medical Sciences, Nepal, showed culture positivity to be 48% and 44.9%, respectively, which is higher in comparison to our study.[3,4] Variations in culture positivity rate of neonatal sepsis in different studies may be due to differences in culture techniques and use of antibiotics before sending investigations. The majority of culture-positive sepsis was among early-onset neonate sepsis and among term newborn.In a similar study done at Kathmandu University Hospital, Nepal, also showed most of the culture proven sepsis were among early onset neonatal sepsis but preterm and low birth weight neonates were commonly infected.[5] The most common clinical manifestation of neonatal sepsis in our study was birth asphyxia (15.2%) and second most common was respiratory distress (13%). However, in studies from KIST Medical College, Nepal (54%), and Patan Hospital (79%) respiratory distress was the most common clinical manifestation which differs from our study.[1,6] The majority of the isolates were Gram positive, similar to the findings of Peterside O et al., in Nigeria, Sharma P et al., in India and Thapa S et al., in Nepal in their studies showed predominant blood culture yield of Gram-positive organisms of which *S. aureus* was the most prevalent.[7,8,9] In contrast, Shrestha et al., Pokharel et al., and a study from Delhi Neonatal Infection Study Collaboration found majority of isolates which were Gram negative which differs from our study.[3,5,10] This difference in isolates from blood culture may be due to the difference in adherence to infection prevention and control measures. However, in contrast, *Klebsiella* species were the most frequent causative organisms of neonatal sepsis in a study done by Pokharel et al., and also similar findings were showed by Shrestha et al.[3,11] This variation in the major isolate may be due to differences in study setting, study population, and adherence to hand hygiene practices.

Our study shows that the majority of causative organisms have developed resistance to the most frequently used antibiotics; amoxicillin and cefotaxime from the beta-lactam group similar to the findings by Pokharel et al., and many other NICUs in other parts of Nepal and Pakistan.[3,7,8,11,12] Furthermore, the isolated *S. aureus* showed 100% resistant to colistin sulfate as well but good sensitivity to higher beta-lactam antibiotics such as meropenem (93.1%) and vancomycin (83.3%). Also, the isolated *Staphylococcus aureus* had 100% sensitivity to linezolid and ampicillin similar to findings showed by Sarangi et al., and Dalal et al., in their studies.[12,13]

Both Gram-positive and Gram-negative organisms showed high susceptibility to carbapenems, a similar finding to other studies conducted both inside and outside Nepal.[14,15] Similarly, Gram-negative organisms showed high susceptibility to

Table 3: Bacteriological profile and antibiotics sensitivity pattern

Drugs	Staphylococcus aureus		Acinetobacter		Enterococcus		Klebsiella		Micrococcus		Total	
	Sen	Res	Sen	Res	Sen	Res	Sen	Res	Sen	Res	Sen	Res
Cefotaxime	11 (40.7)	16 (59.3)	4 (80.0)	1 (20.0)	2 (66.7)	1 (33.3)	-	1 (100.0)	0 (0.0)	1 (100)	17 (47.2)	19 (52.8)
Amikacin	24 (85.7)	4 (14.3)	4 (80.0)	1 (20.0)	2 (50.0)	2 (50.0)	1 (100.0)	-	1 (100.0)	0 (0)	31 (81.6)	7 (18.4)
Piperacillin/ Tazobactam	18 (85.7)	3 (14.3)	4 (66.7)	2 (33.3)	4 (100.0)	0 (0.0)	1 (100.0)	-	1 (100.0)	0 (0.0)	27 (84.4)	5 (15.6)
Vancomycin	20 (83.3)	4 (16.7)	1 (33.3)	2 (66.7)	2 (66.7)	1 (33.3)	-	-	-	-	23 (76.7)	7 (23.3)
Meropenem	27 (93.1)	2 (6.9)	7 (100)	0 (0.0)	3 (100.0)	0 (0.0)	1 (100.0)	-	1 (100.0)	1 (0.0)	38 (95.0)	2 (5.0)
Colistin sulfate	0 (0.0)	2 (100.0)	2 (100)	0 (0.0)	-	-	-	-	-	-	2 (50.0)	2 (50.0)
Imipenem	-	-	-	-	1 (100.0)	0 (0.0)	-	-	-	-	1 (100.0)	0 (0.0)
Linezolid	2 (100.0)	0 (0.0)	-	-	-	-	-	-	-	-	2 (100.0)	0 (0.0)
Amoxiclav	9 (42.9)	12 (57.1)	0 (0.0)	3 (100.0)	2 (100.0)	0 (0.0)	-	-	-	-	11 (42.3)	15 (57.7)
Ciprofloxacin	4 (80.0)	1 (20.0)	-	-	-	-	-	-	-	-	4 (80.0)	1 (20.0)
Ampicillin	3 (100.0)	0 (0.0)	-	-	-	-	-	-	-	-	3 (100.0)	0 (0.0)

Sen: Sensitive, Res: Resistant

colistin, which is consistent with the findings of Jasani Bonny et al., and Pokharel et al., study in Nepal.[3,20] Vancomycin (83.3%) and linezolid showed high (100%) susceptibility toward Gram-positive isolates, similar to the findings of Mulla and Revdiwala, and Singh et al.[18,19] Amikacin showed 85.7% susceptibility against *S. aureus*, 80% against isolated *Acinetobacter*, 100% against *Klebsiella,* and slightly less only 50% against isolated *Enterococcus*. GBS, the most common cause of EOS in high-income countries, has a low reported incidence in low- and middle-income countries.[15] Such low incidence of GBS sepsis in EONS is consistent with our findings. Possible reasons for this could include overuse of antibiotics during the antenatal period or substandard culture techniques and microbiological methods.[16,17] Among the second-line antibiotics, chloramphenicol had low susceptibility (29.3%) against Gram negatives compared to Gram positives (53.8%), whereas ofloxacin had moderate susceptibility (52.6%) to Gram negatives.

Limitations of the study

It was a single-centered, small study population, limited yield of some pathogens, and lack of sensitivity testing to some common and higher antibiotics were all limitations in our study. Hence, large scale with uniform antibiotics sensitivity testing to commonly used including higher antibiotics done for all isolates, multicenter prospective studies are needed to validate our findings.

CONCLUSION

Gram-positive isolates were the predominant pathogens among enrolled neonates at BMCTH. Most of the isolated Gram-positive and Gram-negative isolates showed high resistance to commonly used antibiotics. Growing antibiotic resistance is a matter of great concern. Based on our findings, a combination of cefotaxime and amikacin can be used as first-line therapy. However, cefotaxime only had moderate sensitivity so change to piperacillin-tazobactam and vancomycin or linezolid as second-line therapy can be considered early in case of no improvement or deterioration, or combination of vancomycin and meropenem as third line would be the appropriate empirical therapy at BMCTH. However, the use of the broad-spectrum antibiotics as empirical therapy should be evaluated in the long run and should be used cautiously and modified to narrow spectrum antibiotics, as guided by the culture and susceptibility report at the earliest possible.

Emergence of drug resistance can be prevented by rational use of empirical therapy and discontinuation or step down of therapy when suitable, strict restriction on over-the-counter sale of antibiotics without prescription. Time to time evaluation of the bacteriological profile and their sensitivity pattern with timely revision and upgradation seems important because bacteriological profile and sensitivity seem varying.

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