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NEONATAL SEPSIS IN NICU OF A TERTIARY HOSPITAL – A CHANGING TREND IN CULTURE ISOLATES AND ANTIMICROBIAL SENSITIVITY PATTERN IN BALLARI

Neonatology

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ABSTRACT

Introduction: Neonatal sepsis is a worldwide problem that presents a dynamic challenge to Pediatricians. Globally, it is estimated that 2.4 million neonatal deaths were reported in 2020. **Aims and Objectives:** To determine the bacteriological profile and antibiotic sensitivity pattern of neonatal sepsis done in tertiary care NICU in Govt Medical College Hospital. **Materials and Methods:** It is a retrospective observational study done in NICU, VIMS Hospital, Ballari. Patient records pertaining to blood culture confirmed sepsis cases admitted to the NICU unit from January 2022 to April 2022 were examined. The cases were further categorized into inborn/outborn, EOS/LOS and Multidrug resistance. **Results:** Out of 853 samples, 606 cases were inborn of which only 161 cases are culture positive (26.6%) whereas 247 cases were outborn of which 110 cases are culture positive (44.5%). A total of 271 samples were culture positive (31.77). Overall, most common organisms isolated were CONS and Klebsiella. Out of 127 cases of Gram Positive Isolates, 87 cases (68.5%) were Multidrug Resistant whereas 48 out of 112 gram negative cases (42.86%) were multi drug resistant. **Conclusion:** Our study revealed that CONS and Klebsiella are predominant pathogens. Resistance to commonly used Cephalosporins and Penicillins is rampant in all isolates. Both Gram Positive and Negative bacteria are more sensitive to Amikacin and Ciprofloxacin. However, a word of caution while using Ciprofloxacin in neonates.

KEYWORDS

INTRODUCTION

Neonatal sepsis is a worldwide problem that presents a dynamic challenge to paediatricians. Globally, it is estimated that 2.4 million neonatal deaths were reported in 2020.[1] The current Indian neonatal mortality rate is 20 per 1000 live births and in Karnataka, it is 16 per 1000 live births.[2]

A recent metanalysis estimated the global incidence of neonatal sepsis to be 2824/1 lakh live births, significantly higher than estimates reported in 2018 at 2202/1 lakh live births. Global estimates are largely based on data from high income countries, however morbidity and mortality following neonatal sepsis is greatest low- and middle-income countries.[3]

It can be defined as "a clinical syndrome characterized by systemic signs and symptoms of bacteraemia during the first 28 days of life".[4] It is labelled as "early onset (first 72 hours of life)" and "late onset" (beyond 72 hours of life) sepsis.

Neonatal sepsis is mainly caused by different Gram-positive and Gram-negative bacteria and few cases by fungi like candida species. There is a significant geographical diversity of bacteria causing neonatal sepsis and the spectrum is constantly changing over time, even in the same place.[5-7]

Antibiotic resistance has become a global threat and knowing the causative agents of neonatal sepsis and their antimicrobial sensitivity patterns could enable us to choose appropriate therapy for neonatal sepsis. Targeted antibiotic therapy plays a significant role in reduction of antimicrobial resistance.[5,6]

This study was carried out to determine the bacteriological profile and antibiotic sensitivity pattern of neonatal sepsis in NICU in VIMS Hospital Ballari, so that appropriate antimicrobial policy could be made for effective management of neonatal sepsis.

MATERIALS AND METHODS

This retrospective observational study was done in NICU, VIMS Hospital, Ballari. Patient records pertaining to blood culture confirmed sepsis cases admitted to the New-Born Intensive Care (NICU) unit during January 2022 to April 2022 were examined.

Sepsis was suspected in the presence of temperature instability, lethargy, feeding intolerance, respiratory distress, hemodynamic instability, convulsion, hypotonia, irritability or bleeding diathesis.

Prematurity (< 37 weeks of gestation), low birth weight (< 2500 g), rupture of membrane for more than 18 h (PROM), antepartum fever, foul-smelling liquor were considered as risk factors for neonatal sepsis.

In this study we used BACTEC PEDS PLUS vials (Yellow top-paediatric aerobic) from the neonates suspected of Septicaemia from NICU. We analyzed 853 blood cultures. Antibiotic susceptibility test was done using the Kirby-Bauer disc diffusion method, as per the Clinical and Laboratory Standards Institute (CLSI) guidelines (2014).[8]

Blood Collection: Under strict aseptic conditions, disinfect the venepuncture site using chlorhexidine with 70% alcohol swabs, allowing the site to completely dry. Draw 0.5-1.0 ml of blood and place it in paediatric aerobic bottle. Fill the necessary requisition forms. All the paediatric aerobic bottles were sent to Microbiology laboratory.

Early-onset sepsis (EOS) was defined as sepsis occurring within first 72 h of life, that occurring after 72 h of life was defined as late-onset sepsis (LOS) [9]

Multidrug-resistant (MDR) strains were defined as per international standard definitions for acquired resistance and relative to the panel of antibiotics tested for each isolate, as in vitro non-susceptibility to ≥1 agent in ≥3 antimicrobial categories: Penicillins, Cephalosporins, Beta-lactamase inhibitor combinations, Fluoroquinolones, Aminoglycosides, Tetracyclines, Macrolides and Glycopeptides [10]

Inclusion Criteria

1. All the blood culture positive neonatal sepsis cases admitted to NICU.

Exclusion Criteria

1. Neonates with multiple congenital malformation.
2. Neonates with complex congenital heart disease.

Statistical Analysis

From the case records, gestational age, onset of disease in days, sex, birth weight, inborn/out born cases, identified organisms with sensitive pattern were recorded for analysis using Microsoft excel.

Descriptive summary statistics were used to describe demographic profile of cases, culture identified organisms and sensitive pattern. Distribution of sensitive pattern by gram positive, and gram-negative status were also described.

EpiInfo™ was used for data entry and Statistical Package for Social Sciences (SPSS) version 21 was used for data analysis. Summary of measures were reported as percentage for categorical variables and as

mean with standard deviation for quantitative variables.

RESULTS

During the study period, a total of 853 samples were sent from NICU for Culture and Sensitivity of which 606 were inborn whereas 247 cases were outborn. Out of 606 inborn cases, only 161 cases were positive with a positivity rate of 26.6% whereas 110 outborn cases were positive out of 247 cases (44.5%). A total of 271 samples were positive out of 853 cases with an overall positivity rate of 31.77%.

Table 01: Distribution Of Culture Positive Cases w.r.t Place Of Delivery

	TOTAL CASES	CULTURE POSITIVE CASES	POSITIVITY RATE (%)
INBORN	606	161	26.6%
OUTBORN	247	110	44.5%
TOTAL	853	271	31.77%

Out of 271 positive cultures, 146 (53.9%) cases were of male babies whereas 125 (46.1%) cases were of female babies. A total of 181 (66.8%) cases were preterm babies. On comparing the place of birth, 161 (26.6%) cases were inborn babies whereas 110 (44.5%) were outborn. 105 (38.7%) babies weighed more than 2500 g followed 134 (49.5%) by in range of 1500- 2499g and 32 (11.8%) cases were <1500g.

A total of 214 (78.97%) cases out 271 were delivered by Normal Vaginal delivery (NVD) followed by C-section and Assisted Vaginal Delivery (AVD) 46 cases and 11 cases respectively. No Significant maternal history was seen in 201 cases, whereas history of Premature rupture of membrane was present in 40 (14.76%) cases followed by maternal fever (20 cases) and Foul-Smelling Liquor (10 cases).

Table 02: Demographic Profile Of Culture Positive Neonates.

PARAMETERS		N (%)
SEX	MALE	146 (53.9)
	FEMALE	125 (46.1%)
GESTATION	TERM	90 (33.2%)
	PRETERM	181 (66.8%)
PLACE OF DELIVERY	INBORN	161 (26.6%)
	OUTBORN	110 (44.5%)
WEIGHT	>2500g	105 (38.7%)
	1500-2499g	134 (49.5%)
	<1500g	32 (11.8%)
MODE OF DELIVERY	NVD	214 (79%)
	LSCS	46 (17%)
	AVD	11 (4%)
MATERNAL HISTORY	NO HISTORY	201 (74%)
	PROM	40 (14.76%)
	MATERNAL FEVER	20 (7.3%)
	FOUL SMELLING LIQUOR	10 (3.6%)

Among culture positive sepsis, 159 (58.67%) cases were Early Onset Sepsis (EOS) and 112 cases were Late Onset Sepsis (LOS).On comparing Gram-positive organisms with place of delivery, 79 (62.2%) cases were inborn culture positive cases whereas 48 (37.8%) cases were outborn. Coagulase negative staphylococcus (CONS) was most commonly seen in inborn babies (76 out of 117 cases) as compared to outborn (41 out of 117 cases) whereas Staphylococcus Aureus organism was most commonly seen as outborn (04 cases out of 06 cases). All the Group B Streptococcus (GBS) were outborn (03 cases).

Table 03: Distribution Of Gram-positive Organisms w.r.t Place Of Delivery.

ORGANISMS	NO. OF CASES	INBORN	OUTBORN
CONS	117 (92.1%)	76 (64.96%)	41 (35.04%)
STAPH AUREUS	06 (4.7%)	02 (33.33%)	04 (66.67%)
STREPTOCOCCUS	03 (2.4%)	00	03 (100%)
ENTEROCOCCUS	01 (0.8%)	01 (100%)	00
TOTAL	127 (100%)	79 (62.2%)	48 (37.8%)

Out of 112 Gram negative organisms, 64 (57.14%) cases were Klebsiella, followed by 22 (19.64%) cases of Non-Fermenting Gram Negative Bacilli, 07 (6.25%) cases of Citrobacter, 06 (5.35%) of E. coli and 08 (7.15%) cases of other gram-negative bacteria.

Overall Gram-negative organisms presenting as Early Onset Sepsis (EOS) were seen in 77 (68.75%) cases where as Late of Sepsis were 35 (31.25%) cases. On further comparing the Gram-negative organisms with Onset of sepsis, Klebsiella was most commonly categorized as EONS (43 out of 64 cases) followed by LONS (21 out of 64 cases) whereas both Non- Fermenting Gram Negative Bacilli and Citrobacter most commonly seen as EONS (16 cases and 5 cases respectively). All cases of Acinetobacter presented as EONS (5 cases).

Table 04: Distribution Of Gram-negative Organisms w.r.t Onset Of Sepsis.

ORGANISMS	NO. OF CASES	EOS	LOS
KLEBSIELLA	64 (57.15%)	43 (67.19%)	21 (32.81%)
NON-FERMENTING GRAM NEG BACILLI	22 (19.64%)	16 (72.72%)	06 (27.28)
CITROBACTER	07 (6.25%)	05 (71.43%)	02 (28.57%)
ACINETOBACTER	05 (4.46%)	05 (100%)	00
E. COLI	06 (5.35%)	03 (50%)	03 (50%)
OTHER GRAM NEG. BACTERIA	08 (7.15%)	05 (62.5%)	03 (37.5%)
TOTAL	112 (100%)	77 (68.75%)	35 (31.25%)

On comparing Gram-negative organisms with place of delivery, 65 (58.04%) cases were inborn whereas 47 (41.96%) cases were outborn. Klebsiella was most commonly seen in inborn babies (38 out of 64 cases) as compared to outborn (26 out of 64 cases). Non-Fermenting Gram Negative Bacilli, Citrobacter and Acinetobacter organism were also commonly seen in inborn babies (14 cases, 04 cases and 03 cases respectively). Only E. coli was more common in outborn babies compared to inborn (04 out of 06 cases).

Table 05: Distribution Of Gram-negative Organisms w.r.t Place Of Delivery.

ORGANISMS	NO. OF CASES	INBORN	OUTBORN
KLEBSIELLA	64 (57.15%)	38 (59.37%)	26 (40.63%)
NON-FERMENTING GRAM NEG BACILLI	22 (19.64%)	14 (63.64%)	08 (36.36%)
CITROBACTER	07 (6.25%)	04 (57.14%)	03 (42.86%)
ACINETOBACTER	05 (4.46%)	03 (60%)	02 (40%)
E. COLI	06 (5.35%)	02 (33.33%)	04 (66.67)
OTHER GRAM NEG. BACTERIA	08 (7.15%)	04 (50%)	04 (50%)
TOTAL	112 (100%)	65 (58.04%)	47 (41.96%)

Out of 271 culture positive cases, 32 (11.8%) cases were of fungal origin with candida species seen in all cases. Out of 32 cases, 24 (75%) cases presented as LONS as compared to 08 (25%) cases as EONS. 17 cases were inborn babies whereas 15 cases were outborn.

On comparing the sensitivity pattern for different antibiotics with gram positive organisms, 80% cases are sensitive for amikacin (80 out of 100 cases) followed by 60.9% for cotrimoxazole (14 out of 23 cases). 96.5% resistance was seen with ceftazidime (84 out of 87 cases) followed by 84% for cloxacillin (42 out of 50 cases) and 79.6% for cefotaxime (90 out of 113 cases).

For gram negative organisms, Maximum sensitivity of 74.55% was seen for ciprofloxacin (82 out of 110 cases) followed by 67.64% for amikacin (69 out of 102 cases). Resistance for all the cases was seen with cloxacillin (86 out of 86 cases), cefoxitin (07 out of 07 cases) and ampicillin (6 out of 6 cases).

Table 06: Sensitivity Of Gram-positive Organism And Gram-negative Organism.

ANTIBIOTICS	ORGANISM					
	GRAM POSITIVE			GRAM NEGATIVE		
	(S)	(R)	(I)	(S)	(R)	(I)
Amikacin (AK)	80	16	04	69	30	03
Ceftriaxone (CTR)	25	74	01	27	70	01
Cefotaxime (CTX)	20	90	03	31	77	00
Gentamycin (G)	11	06	04	07	12	00
Ceftazidime (CAZ)	02	84	01	15	90	02
Ciprofloxacin (CIP)	32	73	02	82	26	02
Nitrofurantoin (NIT)	01	00	01	00	00	00
Cotrimoxazole (COT)	14	08	01	04	06	00

Ampicillin (AMP)	01	12	00	00	06	00
Amoxyclav (AMC)	29	59	.7	24	76	02
Norfloxacin (NX)	01	00	00	02	00	00
Cloxacillin (COX)	07	42	01	00	86	00
Cefoxitin (CX)	37	61	03	00	07	00

Out of 127 cases, overall, 87 cases (68.5%) were Multi Drug Resistant in Gram Positive bacteria. 81 (69.2%) Coagulase negative staphylococcus (CONS), 3 (50%) cases of Staphylococcus Aureus, 02 (66.67%) cases of Streptococcus were found to be Multidrug Resistant.

Table 07: Distribution Of MDR Gram Positive Organism.

ORGANISM (N)	FREQUENCY OF MDR ORGANISM (%)
CONS	81 (69.2%)
STAPH AUREUS	3 (50%)
STREPTOCOCCUS	02 (66.67%)
ENTEROCOCCUS	01 (100%)
TOTAL	87 (68.5%)

Out of 112 cases, overall 48 cases (42.86%) were Multi Drug Resistant in Gram Negative cases. 24 (37.5%) cases of Klebsiella, 13 (59.1%) cases of Non-Fermenting Gram Neg Bacilli, 02 (28.6%) cases of Citrobacter were found to be Multidrug Resistant.

Table 08: Distribution Of MDR Gram Negative Organism.

ORGANISM (N)	FREQUENCY OF MDR ORGANISM (%)
KLEBSIELLA	24 (37.5%)
NON-FERMENTING GRAM NEG BACILLI	13 (59.1%)
CITROBACTER	02 (28.6%)
ACINETOBACTER	03 (60%)
E. COLI	02 (33.3%)
OTHER GRAM NEG. BACTERIA	04 (50%)
TOTAL	48 (42.86%)

DISCUSSION

Blood culture remains the gold standard investigation for the diagnosis of neonatal sepsis. To know the bacteriological profile and antibiogram, the present study was conducted retrospectively in blood culture positive neonatal sepsis.

In our study, the overall blood culture positivity rate was found to be 31.77%, these findings were similar to the prevalence rate in various studies conducted by Sundaram V et al[11], Jyothi P et al[12] and Tallur SS et al[13]. While comparing the culture positivity rate of Inborn and Outborn deliveries, it was found that only 26.6% of all the inborn cases were culture positive as compared to 44.5% in outborn deliveries suggesting a good hygienic practice among hospital health care workers.

In the present study, 58% cases presented with early onset sepsis (EOS) as compared to 41% with Late onset sepsis (LOS). EOS cases are comparatively less when compared with studies conducted by Peterside O et al[14] and Muley VA et al[15], who found EOS in 66% and 66.7% cases respectively and LOS in 34% and 33.3% cases respectively. One possible explanation for the difference in results could be because of the routine utilization of antibiotics during obstetric care which might affect the blood culture yield of the neonates as there is significant transplacental transfer of these antibiotics to the foetus.

In the present study, Gram-positive bacteria were the most commonly isolated organisms causing neonatal sepsis followed by Gram Negative bacteria and Fungi, which is in congruent with study reports from Egypt, Uganda and other developing countries.[16,17,18] Overall, the most common organism isolated is Coagulase Negative Staphylococcus (CONS) followed by Klebsiella. Similar CONS predominance was reported by Mohamadi P et al[19], Stoll BJ et al[20] and Sheth KV et al[21].

Coagulase negative staphylococci could be contaminant growths and there are several proposed algorithms for distinguishing between true CONS infections and contaminants[22,23] but no gold standard exists. Usually the presenting signs are nonspecific, hence definitive diagnosis of CONS infection in infants is difficult.[24] Further complicating the diagnosis is the fact that CONS are a component of normal skin flora and thus can potentially contaminate blood cultures drawn peripherally or through venous catheters.[25] The inability to distinguish between infection and contamination can lead to more laboratory tests, longer hospital stays, and unnecessary antibiotic exposures.[26] As proposed by Zaidi et al., a possible solution would be to obtain two peripheral blood cultures at the time of every sepsis evaluation.[22]In the present study, 96.5% gram positive cases were resistant to ceftazidime followed by 84% for cloxacillin and 79.6% for cefotaxime whereas all the gram negative were resistant to cloxacillin, cefoxitin and ampicillin. Resistance rates of isolated Gram-positive bacteria against third generation Cephalosporines were also high in studies from Nigeria, Tanzania, Georgia, Iran and other developing countries[27-31] signifying a global trend towards resistance against commonly used antibiotics due to overutilization of the named drugs as empiric treatment for most other common neonatal problems which were not actually infectious in origin.

For gram negative organisms, maximum sensitivity of 74.55% was seen for ciprofloxacin followed by 67.64% for amikacin whereas for gram positive cases, maximum sensitivity was seen with amikacin (80%). This could be explained by less utilization of these antibiotics for two reasons: First, the antibiotics are used as third line options indicating less utilizations of these agents at NICU. Second, Ciprofloxacin is not validated to use among younger children unless benefit-risk analysis warrants its utilization whereas amikacin is not easily accessible in most centres showing its lower rate of utilization making most isolated bacteria better susceptible to these two antibiotics. These findings are also seen with studies conducted by Barrow et al[27] and Wayne et al[32]. These two drugs could be a potential antibiotic of choice for empiric treatment of neonatal sepsis in the future.

The emergence of MDR bacteria presents a great challenge to the management of neonatal sepsis, causing significant morbidity and mortality. The overall prevalence of neonatal sepsis due to MDR strains in our study was 49.8%. MDR among gram positive and gram negative isolates were 68.5% and 42.86% respectively, which is comparatively lower than the studies conducted by DeNIS Collaboration[33] from India and Labi AK et al[10] from Ghana.

Low prevalence of MDR organisms in our study suggest good hygienic practices among health care workers. Still lower susceptibility of Penicillin group and Cephalosporins among all bacteria create alarming sign for developing Anti-Microbial resistance as they are commonly used drugs for Outpatient based treatment.

CONCLUSION

Our study revealed that the CONS and klebsiella are the predominant organisms. Both gram-positive and gram-negative isolates showed high resistance to commonly used antibiotics. Significant proportions of them were commonly used antibiotics. Such high antibiotic resistance is associated with significant neonatal morbidity and mortality.

The best prevention of neonatal sepsis comprises of early recognition of high-risk infants and strict infection control practices, such as safe delivery, hand hygiene, avoidance of unnecessary invasive procedures and restricted entry to the NICU.

Based on our findings, Both Gram Positive and Negative bacteria are more sensitive to Amikacin and Ciprofloxacin. However, a word of caution while using Ciprofloxacin in neonates.

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