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Original Research Article

Study of etiology and risk factors of neonatal sepsis in a tertiary care hospital in North Karnataka

Advaitha Annapurna Reddy[1], Anand Bhimaray Janagond[2]*, Shivakumar S Solabannavar[2], Ashok Badakali[3]

[1]*S. Nijalingappa Medical College, Navanagar, Bagalkote, Karnataka, India*
[2]*Dept. of Microbiology, S. Nijalingappa Medical College, Navanagar, Bagalkote, Karnataka, India*
[3]*Dept. of Paediatrics, S. Nijalingappa Medical College, Navanagar, Bagalkote, Karnataka, India*

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ABSTRACT

Background: Neonatal sepsis (NS) accounts for around 23% of annual neonatal deaths in India. The aetiopathogenesis of early neonatal sepsis (ENS) and late neonatal sepsis (LNS) vary. This study intends to analyse the associated risk factors associated with NS, bacteria causes, their antibiotic susceptibility patterns, and treatment outcome.

Materials and Methods: In this hospital-based prospective observational study, 102 consecutive cases of NS admitted to NICU were included. Blood samples were cultured in BacT/Alert and bacterial isolates were further processed in Vitek2. Details of potential risk factors were collected using a checklist, and the participants were followed up till recovery/transfer/death. Data was analysed by calculating the proportions, percentages and chi square test.

Results: Participants included 86 ENS and 16 LNS cases. Majority of the ENS (62%) and nearly half of the LNS (55%) cases were born premature. Majority of the ENS (67%) and nearly half of the LNS (47%) cases had low birthweight. Meconium-stained liquor (19%) and premature rupture of membranes (14%) were the commonest perinatal risk factors associated with ENS. Other risk factors noted in NS were poor APGAR score, perinatal asphyxia, intravenous fluid administration (98%) and central venous catheter (22%).

The culture positivity among NS cases was 22%. Staphylococcus spp. was the commonest bacterial pathogen isolated from neonatal sepsis cases, both among ENS and LNS, most of them being methicillin resistant. Klebsiella pneumoniae was the commonest GNB isolated.

Conclusion: Common risk factors associated with neonatal sepsis in general were prematurity and low birth weight. Meconium-stained liquor, and premature rupture of membranes were seen more commonly in ENS. In this hospital, though NS is predominantly caused by MDR bacteria, the treatment outcome is good.

1. Introduction

Neonatal sepsis, accounting for around 22% of annual neonatal death globally and around 23% in India is a major cause of mortality and morbidity.[1] Neonatal sepsis is categorised either as early-onset neonatal sepsis (ENS) when it happens within 72 hours of birth, and as late onset neonatal sepsis (LNS) if it begins after 72 hours and up to a month after birth. ENS is traditionally thought to be caused by organisms like group B Streptococcus and enteric gram-negative bacilli (GNB), acquired peripartum from the maternal genital tract. Contrarily, LNS is considered to

* *Corresponding author*.
E-mail address: dranandj2021@gmail.com (A. B. Janagond).

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occur because of the acquisition of pathogens from the community or during hospitalisation.[2]

Studies have documented incidence of neonatal sepsis to be from 14.3% to 23% in India. ENS accounts for two third of cases and is mostly caused by Gram negative bacilli such as Acinetobacter spp., Klebsiella spp. and E.coli, many of them being multi drug resistant. Among Gram positive bacteria, Staphylococcus spp. is the common pathogen, many strains being methicillin resistant.[3,4]

Out-born admissions, need for artificial ventilation, gestational age <37 weeks and premature rupture of membranes are some of the important risk factors for sepsis among neonates in India. There is a need for robustly designed and reported research to confirm the role of other risk factors of neonatal sepsis in India.[5]

The World Health Organization (WHO) recommends the use of gentamicin with either ampicillin or benzyl penicillin as first-line treatment for neonatal and paediatric sepsis in resource-limited settings, with ceftriaxone as recommended second-line therapy.[6] Due to varying drug resistance patterns in bacteria isolated from different regions, the WHO empirical antibiotic recommendations for neonatal sepsis are likely to be inadequate in many developing countries. Robust AMR surveillance and reporting is necessary to develop region-specific empirical antibiotic recommendations for neonatal sepsis.[7]

The spectrum of pathogenic bacteria and their antibiotic susceptibility patterns causing neonatal sepsis keeps changing temporally and geographically. There is a need to study this pattern periodically to update antibiotic prescription policies and infection control measures at each place in India.[8,9] As the incidence of multidrug resistant bacteria is increasing there is a need to explore sensitivity patterns to newer antibiotics, such as ceftazidime-avibactam and ceftolozane-tazobactam. The present study is proposed to fill this knowledge gap. This study also intends to identify risk factors for neonatal sepsis and clinical outcomes in this region.

2. Materials and Methods

Hospital-based prospective observational study design was followed. The study was conducted after obtaining approval from the Institutional Ethics Committee (IEC) and informed written consent from the parent/guardian of each neonate. Minimum sample size was calculated based on the DeNIS study as 90 with confidence interval of 95%.[4]

Aseptically collected single blood sample from each participant was cultured aerobically using BacT/Alert automated blood culture system. Identification and antibiotic susceptibility testing (AST) were performed for the samples yielding growth using Vitek-2 automated system following standard microbiological protocols. AST for gram positive cocci was performed using P628 card of Vitek-2. AST for gram negative bacilli was performed by using N405/N406 and N407 cards of the Vitek-2. Colistin susceptibility of all gram-negative bacilli was confirmed by colistin agar dilution test as per CLSI M100 guidelines.[10]

Pathogenic nature of the isolates was ascertained by using laboratory parameters available (Total blood count, differential WBC count, CRP, Pro-calcitonin, CSF culture result) and the clinical assessment of the patient; isolates reported as commensals/ contaminants were excluded from further study and analysis. Pathogenic bacterial isolates were classified as MDR/XDR/PDR based on the guidelines mentioned CLSI M100 31st edition.[11]

Data was tested for normality using Kolmogorov-Smirnov (KS) test. Percentages and proportions were used for qualitative data, mean and standard deviation for quantitative data, chi-squared test and Student's t-test were applied.

3. Results

Data was collected from 102 consecutive neonates (<1 month age) admitted to NICU with clinical diagnosis of sepsis. The basic details of the study participants are provided in (Table 1). The gestational age of the participants and their APGAR scores at 5 minutes of birth are displayed in the (Figures 1 and 2).

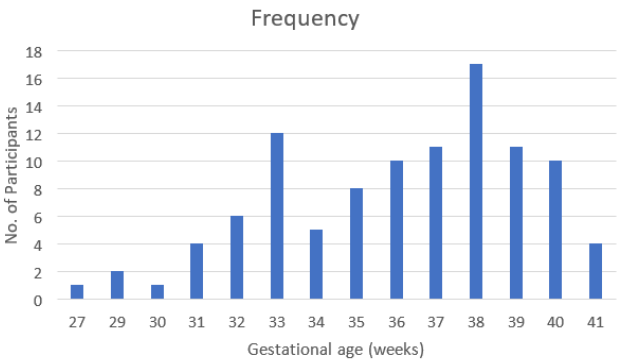

Figure 1: Distribution of participants according to gestational age

The Table 2 compiles the various potential risk factors in ENS and LNS cases, separately among the inborn and out-born cases. Among the 102 participants, only two neonates died, and the cause of death were not related to infection. The Table 3 shows distribution of single, multiple risk factors of sepsis among the groups, and the difference found was not statistically significant.

A total of 22 isolates were obtained from the blood samples, of which 8 were gram negative bacilli and 14 were gram positive cocci. None of the CSF samples yielded growth of organisms.

Table 1: Distribution of neonatal sepsis with respect to gender, type of delivery and place of birth

Features	**Inborn (Born in the study centre)**		**Out born (Born outside the study centre)**	
Gender	**Early Neonatal sepsis**	**Late Neonatal sepsis**	**Early Neonatal sepsis**	**Late Neonatal sepsis**
Males	28	1	24	10
Females	25	1	9	4
Total	53	2	33	14
Vaginal delivery	17	0	21	7
LSCS*	36	2	12	7
Total	53	2	33	14

*LSCS - lower (uterine) segment Caesarean section

Table 2: Distribution of risk factors and outcome in inborn and out-born cases

	Inborn		**Out-born**	
Risk Factors	**Early Neonatal sepsis**	**Late Neonatal sepsis**	**Early Neonatal sepsis**	**Late Neonatal sepsis**
Prematurity (<38 wk.)				
• Extreme prematurity (<28 wk.)	0	0	0	1
• Moderate prematurity (≥28- <32 wk.)	5	0	1	2
• Late prematurity (≥32 - <38 wk.)	27	2	16	6
• ≥ 38 wk.	21	0	16	5
Low Birth weight				
• Very low birth weight (<1.5 Kg)	14	1	4	3
• Low birth weight (≥1.5 -<2.5 Kg)	21	1	10	5
• Total low birth weight (<2.5Kg)	35	2	14	8
• ≥ 2.5 Kg	18	0	19	6
Maternal risk factors				
Maternal infection (Fever)	0	0	0	0
Maternal Steroid administration	2	0	1	2
Gestational diabetes				
Perinatal risk factors				
Meconium-stained amniotic fluid	11	1	5*	0
Premature rupture of membranes (>24 hours)	10	0	2*	0
Poor APGAR score (<7)	4	0	0*	0*
Birth asphyxia	1	1	5*	0
Treatment related risk factors				
Central venous catheter	16	1	7	2
Mechanical ventilation	22	0	15	4
Parenteral nutrition	1	0	3	0
Intravenous Fluids	50	2	32	14
Clinical outcome:				
Cured	51	2	33	14
Death	2	0	0	0
Total	53	2	33	14

*Total will not add up as complete data was not available for some of the participants

Table 3: Comparison of distribution of varying numbers of risk factors among early and late neonatal sepsis cases

		No risk factor	One obstetric risk factor	Two obstetric risk factors	Type II DM	Unknown	Total
Early sepsis	Neonatal	71(82.6%)	8(9.3%)	4(4.7%)	1 1.2%	2(2.3%)	86(100.0%)
Late sepsis	Neonatal	14(87.5%)	0(0.0%)	1(6.3%)	0(0.0%)	1(6.3%)	16(100.0%)
Total		85(83.3%)	8(7.8%)	5(4.9%)	1(1.0%)	3(2.9%)	102(100.0%)

Chi square value= 2.491 p value= 0.646

Table 4: Distribution of isolates among early and late neonatal sepsis cases

Type of sepsis		No isolates	Acineto-bacter buamanii	Enteroc-occus faecium	Escherichia coli	Klebsiella pneumoniae	Staphyloco-ccus aureus	Staphyloco-ccus epidermidis	Staphyloc-occus hemolyticus	Staphyloco-ccus hominis	Total	GNB	GPC
Early Neonatal sepsis	Count	68	2	1	0	5	2	2	1	5	86	7	11
	%	79.1%	2.3%	1.2%	0.0%	5.8%	2.3%	2.3%	1.2%	5.8%	100.0%	8.1%	12.8%
Late neonatal sepsis	Count	12	0	0	1	0	0	0	2	1	16	1	3
	%	75.0%	0.0%	0.0%	6.3%	0.0%	0.0%	0.0%	12.5%	6.3%	100.0%	6.3%	18.8%
Total	Count	80	2	1	1	5	2	2	3	6	102	8	14
	%	78.4%	2.0%	1.0%	1.0%	4.9%	2.0%	2.0%	2.9%	5.9%	100.0%	78.4%	13.7%

GPC- Gram positive cocci, GNB – Gram negative bacilli

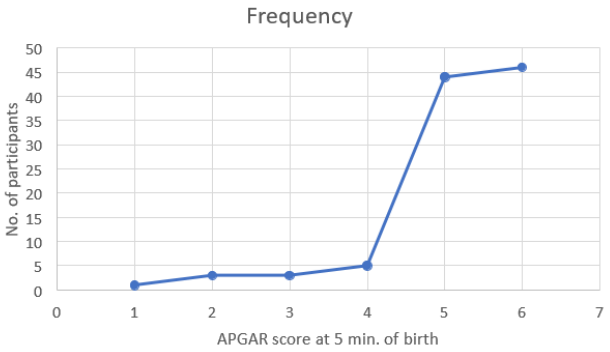

Figure 2: Distribution of participants as per theAPGAR score at 5 minutes of birth

4. Discussion

Out of the 6.9 million neonatal sepsis global burden, South Asia accounts for 3.5 million cases per year.[12] India accounts for a large proportion of this disease burden. Though population-based figures are not available, most of these sepsis-related neonatal deaths are supposed to be taking place in rural areas of India where more than 60% of the Indian population resides.[9,13]

The present study included 86 ENS cases and 16 LNS cases. Among the participants, nearly half were inborn (55) and the remaining were out-born (47). The incidence of early neonatal sepsis was much higher than the late neonatal sepsis, both in the inborn (53/55) and out-born cases (33/47). Majority of inborn cases were delivered by LSCS (38/55) and nearly a third of out-born cases with sepsis were delivered by LSCS (17/47, 36%). This difference could be because of people choosing higher medical facility like the medical college hospital when LSCS is indicated or expected based on antenatal assessment.

4.1. Risk factors for neonatal sepsis

Majority of the ENS (34/55, 62%) and nearly half of the LNS (26/47, 55%) cases were born premature. Majority of the ENS (37/55, 67%) and nearly half of the LNS (22/47, 47%) cases had low birthweight. Prematurity and LBW are described as risk factors for early and late NS in several studies.[4,11]

Meconium-stained liquor (19%) and premature rupture of membranes (>24 hours) (14%) were the most common perinatal risk factors associated with ENS. Other risk factors noted in neonatal sepsis were poor APGAR score at 5 minutes of birth and perinatal asphyxia. All these are well accepted perinatal risk factors for neonatal sepsis.[4,11] Among the neonatal treatment related risk factors, intravenous fluid administration (98%) and central venous catheter (22%) were the commonest risk factors. The difference among the ENS and LNS for any of the risk factors was not statistically significant in this study.

4.2. Culture positive sepsis

The overall culture positivity among neonatal sepsis cases was 22%; 21% for ENS and 25% for LNS cases. A Similar study done in New Delhi has reported isolation rates of 43%.[4] The lower isolation rates in the present study could be because only one blood sample was used for culture, and many out-born cases had received antibiotics before collection of the sample. Multiple blood cultures along with CSF culture in suspected cases of meningitis, samples collected with aseptic procedures before administering antibiotics would increase the isolation rates.[14,15]

4.3. Spectrum of isolates and their antibiotic susceptibility

Overall, gram positive cocci (GPC) (13.7%) were isolated from more cases than gram negative bacilli (GNB) (7.8%). Among ENS GPC were isolated from 12.8% and GNB from 8.1% of cases. Among LNS cases, GPC were isolated from 18.8% and GNB from 6.3% of cases. Several studies have documented GNB as common cause of ENS and GPC as common cause for LNS.[4,11] In this study, more number of GPC isolated from ENS could be because, some of the GPC could be skin commensals or contaminants as pathogenicity could not be ascertained for Coagulase Negative Staphylococcus spp. (CONS) with single blood sample culture. If multiple blood cultures yield the same CONS then it confirms the pathogenicity. Studies have reported CONS as the predominant organism causing LNS.[4]

Among the GNB isolated, most were isolated from ENS. This finding is similar to several other studies.[11] Klebsiella spp., E.coli and Acinetobacter spp. are described as the commonest bacterial pathogens isolated from ENS. Klebsiella pneumoniae was the commonest GNB isolated in this study. Acinetobacter spp. is identified as the commonest isolate in a New Delhi based multi-centric study.[4] Studies have shown variations among common pathogenic GNB in ENS, which is expected to change from place to place, and time. Thus, it is important to conduct studies regularly to know the changing spectrum of organisms. ENS is believed to be caused by organisms to which the neonate is exposed during the process of childbirth.[4,11] Most of the isolates were found to be MDR and some XDR; none of the isolates were PDR.

Among Staphylococcus spp., except one isolate all were methicillin resistant, making most of the beta-lactam antibiotics ineffective against them. All the Staphylococcus spp. were found to be sensitive to linezolid, vancomycin, daptomycin and teicoplanin; many were sensitive to tigecycline and chloramphenicol though these antimicrobials are not recommended in blood stream

infections. Vancomycin was used to treat most of the study participants. Studies have reported increasing incidence of drug resistant pathogens causing neonatal sepsis posing a major treatment challenge.[4,5,11]

Among the six Enterobacterales, four were MDR and one each was non-MDR and XDR. Most of them were carbapenem-resistant strains, and were not susceptible to beta lactam/beta lactamase inhibitor combinations, including Ceftazidime/ Avibactam and Ceftolozane/ Tazobactam tested in the additionally used N407 Vitek-2 card. Most of the GNB isolates were susceptible to tetracycline, tigecycline and chloramphenicol, but these are not recommended for blood stream infections. Thus, additional usage of N407 card panel did not help much in deciding antibiotic to treat sepsis in this study. As many antibiotics present in N405/N406 are also present in N407 card, it seemed like unnecessary duplication of testing and cost. Practically simple methods based on disk elution and disk stacking are available for detecting synergy between cefatzidime-avibactum and aztreonam, which are also recommended by CLSI.[10,15,16] Colistin was used to treat most of the cases of sepsis from which GNB were isolated in this study.

The antimicrobial resistance among bacteria causing neonatal sepsis in the Indian community was not high in 2017, more than 70% S. aureus and K. pneumoniae were reported to be sensitive to commonly used antibiotics.[9] Studies have shown that neonatal sepsis is increasingly caused by MDROs.[17] In general, mortality due to MDRO sepsis is significantly higher as compared to non MDRO sepsis. Common morbidities associated with neonatal sepsis are prolonged use of total parenteral nutrition, need for central venous catheter, invasive ventilation, prolonged hospital stay and neurologic sequelae.[3] Studies have shown that the most severe forms of neonatal sepsis with an unfavourable outcome were due to virulent strains of K. pneumoniae.[18] In sepsis by MDROs, the economic burden is exponentially increased.[3] Novel prediction modelling approaches were evaluated and were found to detect neonatal sepsis early by using maternal, neonatal and laboratory predictors, these are promising approaches that might be useful to clinicians to start treatment early in the future.[19]

Although there is no consensus on the exact modalities, various home-based regimens of empiric injectable and oral antibiotics are promoted in many developing country settings, including India.[20] ICMR provides treatment guidelines for common syndromes in adults including sepsis, but does not specify empirical antibiotic therapy for neonatal sepsis. ICMR recommendation for adult sepsis with unknown aetiology is imipenem/meropenem with or without amikacin, vancomycin/teicoplanin. De-escalation is advised based on antibiotic susceptibility results.[21] Considering that the neonatal sepsis is increasingly caused by MDROs, the World Health Organization (WHO) guidelines for the management of neonatal sepsis, which is currently gentamicin plus ampicillin, needs to be updated.[22] A need for the WHO to develop a neonatal priority antibiotic development list has been proposed with the develop international, interdisciplinary consensus for an accelerated neonatal antibiotic development programme.[22]

5. Limitations of the study

The use of single blood sample culture which probably lead to lower isolation rates and to some extent inability to confirm pathogenicity of some of the isolates were limitations of the study. The primary cause of death in these cases were congenital malformations and not neonatal sepsis. As most of the cases got cured and the outcome was not much variable, analysis to compare antibiotic resistance and outcome could not be done.

6. Conclusion

Common risk factors associated with neonatal sepsis in general were prematurity and low birth weight. Perinatal factors like meconium-stained liquor, and premature rupture of membranes were seen more commonly in ENS.

Isolation rate from blood culture was 22%. Staphylococcus spp. was the commonest bacterial pathogen isolated from neonatal sepsis cases, both among ENS and LNS. Most GNB were isolated from ENS and Klebsiella pneumoniae was the commonest GNB isolated. Drug resistance was high among the isolates with most of them being MDR. Outcome was good with only two deaths out of 102 cases.

7. Ethical Approval

In this study approval from the Institutional Ethics Committee (IEC) was taken under SNMC/ECHSR/2023/A-13/1.0

8. Source of Funding

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9. Conflict of interest

None.

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Author biography

Advaitha Annapurna Reddy, Student

Anand Bhimaray Janagond, Professor https://orcid.org/0000-0003-1820-8558

Shivakumar S Solabannavar, Professor and Head https://orcid.org/0009-0009-8784-8322

Ashok Badakali, Professor and Head https://orcid.org/0000-0003-4105-7284

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