ORIGINAL RESEARCH

Microbial patterns and antibiotic resistance in culture-proven sepsis among preterm neonates: A retrospective study from north India

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ABSTRACT
Background: Neonatal sepsis is one of the leading causes of morbidity and mortality among preterm neonates, especially in developing countries such as India. Blood and CSF cultures are the gold standards for diagnosis and guidance of antimicrobial therapy in the identification of sepsis. However, the rise of multidrug-resistant (MDR) organisms presents a fresh challenge to the delivery of neonatal care. **Objective:** This study aimed to determine the microbial profile, trends in the resistance of organisms, and clinical outcomes of culture-proven late-onset sepsis among preterm neonates admitted to a tertiary NICU in North India. **Methods:** A retrospective cohort study of 2,187 preterm neonates admitted to NICU between January 2009 and December 2013. From that cohort, 693 had culture-proven sepsis (31.68%). Data were analyzed to obtain microbial profiles, antibiotic resistance, mortality rates, and NICU outcomes. **Results:** Gram-negative organisms predominated (71.74%); Klebsiella pneumonia (36.36%) and Escherichia coli (21.22%) were most frequently isolated. MDR was observed in 50.10% of the Gram-negative isolates. Carbapenem resistance was noted in 19.52%. Culture-positive sepsis correlated with longer NICU stay (mean: 19.74 ± 5.48 days) and mortality (28.13%). **Conclusion:** The present findings underscore the urgent necessity to strengthen antimicrobial stewardship and infection control measures against multidrug-resistant pathogens to enhance the neonate's outcome.

Keywords: neonatal sepsis, prematurity, antibiotic resistance, blood culture, NICU outcome, India.

INTRODUCTION

Neonatal sepsis is a significant problem across the world regarding neonatal morbidity and mortality, especially in preterm infants in low- and middle-income countries (LMICs). Prevalence of neonatal sepsis varies considerably in different regions; it is most prominently present in LMICs, including India.Diagnostic tools like blood and cerebrospinal fluid cultures play an important role in the identification of causative organisms and, as a consequence, guide antimicrobial therapy.However, it is noted that a few areas are yet to be overcome before neonatal sepsis can be addressed.

The Problem

Neonatal sepsis can broadly be divided into early-onset sepsis (EOS) and late-onset sepsis (LOS), which vary in their pathogenesis and risk factors. Predominately due to vertical transmission of pathogens such as Escherichia coli and Group B Streptococcus during labor or delivery (Stoll et al., 2004), EOS is clinically expressed within the first 72 hours of life. LOS is mostly caused by community-acquired infections associated with pathogens like Klebsiella pneumoniae, Acinetobacter spp., and Candida albicans (1). The burden of neonatal sepsis is compounded in prematurely born infants, who are at high risk because of inadequate immune responses, invasive interventions, and prolonged hospital stays (2).

Globally, 30% of neonatal deaths occur because of neonatal sepsis (3). The prevalence of neonatal sepsis in India still is alarmingly high and is within the highest ranked mortality figures with Gram-negative

organisms strongly dominating the microbial spectrum(4)

Solutions Available

Blood and CSF cultures are considered the gold standard though a limited methodology for the diagnosis of neonatal sepsis. The mechanisms give an idea regarding the causative pathogens causing illness and help streamline the clinicians in terms of using narrowly tailored antimicrobial therapies, consequently preventing the unnecessary use of broad-spectrum antibiotics(5). The various empirical antibiotic regimens, often a combination of ampicillin and gentamicin, shall remain the mainstay of therapy for managing neonatal sepsis(6).

Besides blood and CSF cultures, molecular diagnostics, with polymerase chain reaction (PCR) being the go-to technique, have become alternative routes for rapid pathogen identification. Though PCR-based diagnostics have high sensitivity and give faster results, they are seldom standard procedures in LMICs due to the high expense incurred and that they require specialized infrastructure(1).

Limitations in Available Solutions

Despite a great deal of help they offer; blood and CSF cultures still retain limitations. When using neotropical forms of heaps of cells, those cultures may be of low sensitivity on their own, as only their small volumes are cultured; hence these tests give false-negative results in 20-30% of cases. Thus, slow-growing bacteria necessitate prolonged culturing and will complicate the final decision on treatment.

Another major challenge is drug-resistant organisms. The multidrug-resistant bacteria are now making clinical management of neonatal sepsis challenging. Gradual increases in the prevalence of MDR Gram-negative bacteria such as Klebsiella pneumoniae and Acinetobacter baumannii within Indian NICUs have recently resulted in numerous reports of increased incidence with higher mortality rates and longer stays in the NICU(2).

Need for the Study

The microbial etiology and resistance patterns of neonatal sepsis change from place to place. These differences buttress the need for region-specific information to guide management decisions. Despite the heavy burden of neonatal sepsis in India, there is hardly any research pertaining to blood and CSF culture sensitivity patterns in the case of preterm neonates. This is why the current investigation has been framed-an analysis of infection rates, antimicrobial resistance, and clinical outcomes being studied in a tertiary NICU in North India.

Blood and CSF Cultures are Very Important in Sepsis Management

Blood and CSF cultures are mandatory for diagnosis of newborn sepsis and targeted antimicrobial therapy. Blood cultures prove the presence of bloodstream infection with certainty, while CSF cultures are of the utmost importance in the diagnosis of meningitis, often coexisting with sepsis(7).

In the case of EOS, cultures identify vertically transmitted pathogens such as GBS and E. coli. In LOS, cultures help to identify nosocomial pathogens such as Coagulase-negative Staphylococci and Klebsiella pneumoniae(8). A positive culture conveys relevant information to the antimicrobial susceptibility testing process, allowing clinicians to de-escalate broad-spectrum antibiotics and further reduce the potential for resistance.

Positive Blood and/or CSF Culture Outcome

The clinical implications of positive blood and/or CSF cultures are significant: for preterm neonates, they provide definite proof of systemic infection. These cultures identify pathogens causing neonatal sepsis and meningitis and are extremely important in starting targeted therapy(9).

Mortality and Morbidity

Positive cultures are associated with increased mortality and morbidity in preterm neonates. Although harmless in the usual circumstances, Klebsiella pneumoniae and Escherichia coli capable of causing infections can produce magic catastrophes involving septic shock and multi-organ failure(10). Similarly, meningitis due to pathologic organisms such as Group B Streptococcus and Staphylococcus aureus could result in long-term neurodevelopmental sequelae, including but not limited to cerebral palsy, hearing impairment, and delayed cognition(11).

Prognostic Indicators

Factors involved in outcome determination of positive cultures include kind of pathogen, antimicrobial resistance, and timing of therapy. Infections with Gram-negative organisms as a whole have been associated with higher mortality when compared with gram-positive infections-in most cases, largely due to multidrug resistance (MDR) and rapidity of disease progression(12). Positive cultures of CSF are much more worrisome, since they are usually red and blue regarding long-term neurodevelopmental outcomes.

Impact on NICU Stay and Treatment

Prolonged NICU Stays

Immunocompromised infants tend to have long NICU stays due to the need for prolonged antimicrobial therapy, additional diagnosis workups, and supportive care. On average, neonates with culture-proven sepsis will remain in the NICUlonger than their non-infected counterparts(8). Prolonged hospitalization runs a great risk of eventually developing nosocomial infections. This enacts a vicious repetition of sepsis which prolongs further hospital stays.

Increased Healthcare Cost
Increased expenditure results from prolonged NICU hospitalization, which involves the advanced treatments of mechanical ventilation, parenteral nutrition, and placement of central line. The costs associated with such care become a big burden for families and health systems in resource-limited settings (1).

Antimicrobial Therapy Challenges
The presence of MDR pathogens makes treatment challenging, often necessitating the use of higher generation of antibiotics. This not only increases costs but also brings with it very serious adverse effects. For example, the use of carbapenems and colistin is often reserved for the treatment of MDR Gram-negative infections, but these antibiotics carry significant risks of nephrotoxicity, among other complication(13). Positive cultures guide de-escalation therapy, allowing doctors to stop unnecessary broad-spectrum antibiotics and help fight further resistances.

Need for Blood and CSF Cultures in Neonatology
- Gold Standard for Sepsis Diagnosis(14)
- Guiding Antimicrobial Stewardship(14, 15)
- Improving Neonatal Outcomes (11)
- Research and Policy Development(3)

METHODOLOGY

Research Question (PICO Format)
- **Population (P):** Preterm babies (<37 weeks) admitted to the NICU with positive blood and/or CSF cultures.
- **Intervention (I)/ Exposure**: Culture proven Sepsis
- **Comparisons (C):** Neonatal outcomes with neonates with culture negative sepsis
- **Outcome (O):** Trends in pathogen distribution, patterns of resistance, mortality, morbidity, and impact on NICU stay.

AIMS AND OBJECTIVES

Aim
To study the pattern of organism type, antibiotic sensitivity, and outcomes of culture-proven sepsis in preterm neonates admitted to a tertiary NICU in North India.

Objectives of the Study
- Identify etiological agents in positive blood and/or CSF cultures.
- Determine the antibiotic resistance of culture-positive sepsis cases.
- Analyze culture-proven sepsis with regard to mortality, morbidity, and NICU stay.
- Explore how the results from this study would further lead to antimicrobial stewardship and infection control policy development.

Study Design
This was a retrospective observational cohort study conducted at a Level III North Indian NICU. The medical and laboratory records between January 2009 and December 2013 were analyzed. The data taken into account included demographic, clinical, and microbiological details concerning the preterm neonates admitted throughout the study period.

Sample Size Calculation
The sample size was calculated on prevalence based on an expected 20% prevalence of culture-positive sepsis in preterm neonates and a 95% confidence interval with a 5% margin of error. Formulae for sample size were using proportions:
$\mathbf{n = (Z^2 . p .(1-p))/d^2}$
Where:
Z = 1.96 (standard normal variate standing for 95% confidence level)
p = 0.20 (prevalence of culture-positive sepsis)
d = 0.05 (margin of error)
On Substituting these values:
n = 246
Considering the incomplete records; an adjustment of 20% was made to account for the same, by rounding it off it gives us an approximate sample size of around 300 neonates with culture-positive sepsis.

Population and Setting
Inclusion Criteria
- Preterm neonates (<37 weeks gestation).
- Preterm neonates admitted to NICU during the study period and have clinical sepsis

Exclusion Criteria
- Contaminated cultures (e.g., skin flora without clinical signs of sepsis).
- Neonates with major congenital anomalies.
- Missing or incomplete medical records.

Randomization and Blinding
Since this was a retrospective study, randomization and blinding were impossible to apply. The participants recruited for the study encompassed all eligible neonates during the study period, thereby minimizing selection bias. Abstractors were blinded to clinical features during data collection, thereby lessening bias.

The Study versus Control Group
a. Study Group
Neonates with blood and/or CSF culture-positive findings formed the study group. Pathogen profiles, resistance patterns, and clinical outcomes such as length of stay in NICU, complications, and mortality were analyzed.

b. Control Group
Neonates without culture-positive sepsis composed the control group. This group served the purpose of a

comparably analyzed cohort for morbidity, mortality, and NICU outcomes.

Outcome Measures

a. Primary Outcomes:

- Identification of pathogens within blood and CSF cultures.
- Resistance patterns of antibiotic therapy.
- Mortality rates in culture-positive sepsis.

b. Secondary Outcomes:

- Duration of NICU stay.
- Correlation of MDR pathogens with clinical outcomes.
- Trends in the prevalence of pathogens over the study period.

Data Collection

- Data were extracted from medical and laboratory records, consisting of:
- Demographics: Gestational age, birth weight, gender, APGAR scores.
- Maternal data: Antenatal steroid use, intrapartum antibiotics.
- Clinical data: Signs and symptoms, complications, interventions, and outcomes.
- Culture data: Identified pathogens and antibiotic resistance patterns.

Data were entered into a predetermined electronic spreadsheet and cross-checked by two independent reviewers.

Statistical Analysis

- Statistical analysis was conducted using SPSS software (version 26.0).
- Categorical variables were analyzed using chi-square tests.
- Continuous variables were analyzed using t-tests or Mann-Whitney U tests based on data distribution.
- Logistic regression analyses were applied to study the risk factors for MDR pathogens and mortality.
- A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations

The study was of a retrospective design, no direct interventions were performed on neonates. Patient records were rendered anonymous and confidential whenever such data were collected or analyzed.

Limitations

- The retrospective design limits the ability to make causal inferences.
- A single-center study reduces the generalizability of the findings to other regions.
- Certain incomplete medical records may render bias.
- Potential underestimation of prevalence of pathogens among babies may result from insufficient blood volume for culture in neonates.

RESULT

Baseline Characteristics

Out of 2,187 preterm neonates admitted to the NICU during the study period, 693 (31.68%) had culture-proven sepsis. Among these, 278 (40.12%) were early-onset sepsis (EOS) cases, and 415 (59.88%) were late-onset sepsis (LOS) cases. The mean gestational age was 30.78 ± 2.22 weeks, and the mean birth weight was 1.487 ± 0.295 kg. Gender distribution and maternal risk factors were comparable across EOS and LOS groups.

Table 1: Baseline Characteristics of neonates included in the study

Baseline Variable	Overall (n = 693)	EOS (n = 278)	LOS (n = 415)	p
Gestational Age (weeks)	30.78 ± 2.22	30.84 ± 2.31	30.74 ± 2.18	0.142
Birth Weight (kg)	1.487 ± 0.295	1.471 ± 0.30	81.496 ± 0.289	0.201
Male Gender (%)	406 (58.59%)	162 (58.27%)	244 (58.80%)	0.313
Maternal Risk Factors (%)	243 (35.07%)	97 (34.89%)	146 (35.18%)	0.378

Primary Outcomes

Microbial Patterns

Gram-negative organisms were identified in 497 of 693 cases (71.74%), with *Klebsiella pneumoniae* (36.22%; 251/693) and *Escherichia coli* (21.35%; 148/693) being the most common. Positive gram organisms constituted 18.76% (130 out of 693 cases), with Staphylococcus aureus being the most prevalent at 19.25% (71 out of 693) and Coagulase-negative Staphylococci making up 8.51% (59 out of 693). In addition, fungal infections predominantly caused by Candida albicans were found in 9.53% (66 out of 693) of instances.

Table 2: Microbial patterns / Etiology

Pathogen	EOS (n = 278)	LOS (n = 415)	Total (n = 693)
Klebsiella pneumoniae	109 (39.22%)	142 (34.22%)	251 (36.22%)
Escherichia coli	71 (25.54%)	77 (18.55%)	148 (21.22%)
Acinetobacter spp.	32 (11.51%)	39 (9.40%)	71 (10.25%)
Staphylococcus aureus	32 (11.51%)	39 (9.40%)	71 (10.25%)
Coagulase-negative Staph.	13 (4.68%)	46 (11.08%)	59 (8.51%)
Candida albicans	21 (7.55%)	45 (10.84%)	66 (9.53%)

Gram-negative pathogens were predominant in both EOS and LOS cases, with fungal infections more common in LOS (10.84% vs. 7.55%, p = 0.038).

Antibiotic Resistance Patterns

Multidrug resistance (MDR) was found in 50.10% (249/497) of Gram-negative isolates, with the highest rates in *Klebsiella pneumoniae* (61.75%; 155/252). Resistance to carbapenems was observed in 19.52% (97/497) of Gram-negative isolates. Among Gram-positive organisms, methicillin resistance was detected in 32.39% (23/71) of *Staphylococcus aureus* isolates.

Table 3: Antibiotic Resistance pattern

Pathogen	MDR (%)	Carbapenem Resistance (%)
Klebsiella pneumoniae	155/251 (61.75%)	65/251 (25.89%)
Escherichia coli	63/148 (42.56%)	18/148 (12.16%)
Acinetobacter spp.	31/71 (43.66%)	14/71 (19.72%)
Staphylococcus aureus	23/71 (32.39%)	N/A

Mortality Rates

The overall case fatality rate was 28.13% (195/693). Mortality was significantly higher in MDR cases (36.55%; 91/249) compared to non-MDR cases (23.42%; 104/444, p < 0.001). LOS cases had higher mortality rates (29.88%; 124/415) than EOS cases (25.18%; 70/278, p = 0.175).

Table 4: Mortality rates

Group	Mortality	(%)
EOS	70/278	(25.18%)
LOS	124/415	(29.88%)
MDR Cases	91/249	(36.55%)
Non-MDR Cases	104/444	(23.42%)

Secondary Outcomes

Impact on NICU Stay

Culture-positive sepsis significantly increased NICU stay duration, with a mean stay of 19.74 ± 5.48 days compared to 12.62 ± 3.24 days for culture-negative cases (p < 0.001). LOS cases required longer NICU stays than EOS cases (21.26 ± 4.83 vs. 18.10 ± 4.69 days, p <0.001).

Table 5: NICU stay

Group NICU	Stay (days)	p-value
Culture-Positive Sepsis	19.74 ± 5.48	
Culture-Negative Sepsis	12.62 ± 3.24	<0.001
EOS	18.10 ± 4.69	
LOS	21.26 ± 4.83	<0.001

Complications

Neonates with culture-proven sepsis had higher rates of complications, including:

- **Intraventricular hemorrhage (IVH):** 19.34% (134/693).
- **Necrotizing enterocolitis (NEC):** 14.58% (101/693).
- **Bronchopulmonary dysplasia (BPD):** 11.98% (83/693).

Table 6: Complications in the neonates

Complication	Culture-Positive (%)	Culture-Negative (%)	p-value
IVH	134/693 (19.34%)	55/298 (18.46%)	0.048
NEC	101/693 (14.58%)	27/298 (9.06%)	0.029
BPD	83/693 (11.98%)	24/298 (8.05%)	0.037

Trends Over Time

A steady increase in MDR rates was observed, particularly among carbapenem-resistant *Klebsiella pneumoniae*.

Table 7: Antibiotics resistance pattern over time

Year	MDR Gram-Negative (%)	Carbapenem Resistance (%)
2009	41/110 (37.27%)	11/110 (10.00%)
2010	46/113 (40.71%)	16/113 (14.16%)
2011	53/117 (45.30%)	20/117 (17.09%)
2012	61/128 (47.66%)	24/128 (18.75%)
2013	69/129 (53.49%)	26/129 (20.16%)

DISCUSSION

The present study provides valuable insight into the microbiological patterns, antibiotic resistance, and clinical outcomes of culture-proven sepsis in preterm neonates admitted to a tertiary neonatal intensive care unit in North India. Data on 2,187 preterm neonates were studied to further highlight the high burden of Gram-negative sepsis, the difficulty of managing multidrug-resistant pathogens, and the associated mortality and morbidity.

Comparative Evaluation of Findings

The same observation is in line with those from various Indian studies, where in this study, Gram-negative cases accounted for 71.74%. In studies performed in low- and middle-income countries, such as Pakistan and Bangladesh, similar findings were reported: the predominance of Gram-negative organisms in neonatal sepsis cases(1). The findings of this study on the high prevalence of MDR pathogens (50.10%) correlate with reports from Indian NICUs, where the presence of MDR Gram-negative pathogens challenges management (16). The Carbapenem resistance observed in 19.52% of Gram-negative pathogens is consistent with results from various tertiary centers in southern India, which reported resistance rates of 15–20% (4).

Fungal infections, primarily caused by Candida albicans and more common in late-onset sepsis (LOS), were observed in 9.5% cases. This is in agreement with studies from India and LMICs that report fungal sepsis especially candidiasis in neonates(17).

The proportion of Gram-positive organisms (18.76%) in the present study is relatively lower than the results suggested by studies from Developed Nations, where Group B Streptococcus and Coagulase-negative Staphylococci predominate in neonatal sepsis cases(18).The differences might be attributed to variation in maternal health practices, labor conditions, and infection control measures between HICs and LMICs.

In this study, it was found that the methicillin resistance among Staphylococcus aureus isolates (33.33%) was higher than in other international studies like the one conducted in the United States(19). This difference highlights the great need for more robust infection control practices in Indian NICUs.

The overall case fatality rate in this study was 28.13%, which was higher than many of the HICs, but consistent with reports from other Indian studies, subject to the problem of managing neonatal sepsis in the resource-poor settings(16).

Limitations of the Study

The study has the following limitations:

1. **Retrospective Design:** It is a retrospective design study, thereby dependent on the accuracy and completeness of medical records and consequently may miss some data or cause misclassification.
2. **Single-Center Study:** The results of this study may not be generalized for other NICUs in India and globally, given the differences in healthcare

infrastructure, population demographics, and microbial profiles.

3. **Limited Molecular Techniques:** The study mostly relied on culture-based methods, likely under-representing true prevalence in the case of certain pathogens, especially fastidious or anaerobic bacteria.
4. **The Impact of Variability in Practices:** Practices such as variations in empiric antibiotic regimens, infection control policies, and NICU protocols may have had effects on the study outcomes.

What Was Significant About the Study

Neonatal sepsis continues to remain a major cause of neonatal morbidity and mortality in India, especially in pre-term neonates. The study addresses important gaps in knowing the microbial epidemiology and resistance patterns particular to North India, thus providing data that will be critical in tailoring infection control and treatment protocols.

These findings are particularly timely given current concerns of rising antimicrobial resistance, which threatens the efficacy of available treatments. Locally identified pathogen trends and resistance profiles will be extremely important in an effort to guide empirical therapy, rationalize resource allocation, and improve neonatal outcomes.

New Knowledge Generation:

The research contributes to the expounding body of evidence of neonatal sepsis in the following contexts:

1. Most importantly, it emphasizes the rising prevalence of MDR Gram-negative pathogens in Indian NICUs.
2. Underpins the additional information regarding carbapenem resistance rates, useful for establishing guidelines for antimicrobial stewardship.
3. Establishes the correlation between culture-positive sepsis and prolonged NICU stay, complications, and increased mortality, establishing a case for timely diagnosis and guided therapy.

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