

Prospective evaluation of c-reactive protein as a diagnostic biomarker with correlation to blood culture and antibiotic susceptibility patterns in neonatal sepsis: A cross-sectional study.

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Abstract

Background

Neonatal sepsis remains a major cause of neonatal morbidity and mortality. Its clinical features are often nonspecific, while blood culture, although definitive, has delayed turnaround and variable yield. C-reactive protein (CRP) is a simple acute-phase marker that supports early decision-making when correlated with microbiological findings.

Objectives

To evaluate the diagnostic utility of CRP in suspected neonatal sepsis and correlate CRP status with blood culture positivity and antimicrobial susceptibility patterns.

Methods

This prospective cross-sectional study was conducted from January 2024 to December 2024 in the Neonatal Intensive Care Unit of Government General Hospital, Suryapet, a tertiary care teaching hospital attached to Government Medical College, Suryapet, Telangana, India. A total of 302 neonates with suspected sepsis were enrolled. Blood samples were collected aseptically before antibiotic administration for CRP estimation and culture. Quantitative CRP was measured using the RHELAX-CRP latex agglutination method, with >6 mg/L considered elevated. Blood cultures and antibiotic susceptibility testing were performed using standard microbiological methods and CLSI guidance.

Results

Among 302 neonates, 178 (58.9%) were males, 186 (61.6%) had low birth weight and 164 (54.3%) were preterm. Blood culture was positive in 70 neonates (23.2%). Gram-negative bacteria predominated, comprising 48 isolates (68.6%), with *Klebsiella pneumoniae* as the commonest isolate. Elevated CRP was observed in 50 culture-positive neonates. CRP showed 71.4% sensitivity, 92.2% specificity, 73.5% positive predictive value and 91.5% negative predictive value. Elevated CRP was significantly associated with culture positivity ($p < 0.001$). Gram-negative isolates showed high resistance to cefotaxime and ceftriaxone, with better sensitivity to imipenem and piperacillin-tazobactam.

Conclusion

CRP is a useful adjunctive marker for neonatal sepsis, especially due to its high specificity and strong culture correlation.

Recommendations

CRP testing should complement blood culture to guide early antibiotics and strengthen NICU antimicrobial stewardship.

Keywords: Neonatal sepsis; C-reactive protein; Blood culture; Antibiogram; Antimicrobial resistance; Neonatal Intensive Care Unit

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Introduction

Neonatal sepsis is a life-threatening systemic infection occurring during the first 28 days of life and continues to contribute substantially to neonatal morbidity and mortality, especially in low- and middle-income settings [1,2]. Early-onset sepsis usually occurs within the first 72 hours of life and is commonly linked to vertical transmission, while late-onset sepsis occurs after this period and is frequently associated with hospital exposure, invasive care and community-acquired infection [3,4].

The diagnosis of neonatal sepsis is difficult because the early clinical signs are subtle and overlap with several non-infectious neonatal conditions. Poor feeding, lethargy, temperature instability, respiratory distress, apnea and irritability are common but nonspecific findings. Because delay in treatment can be harmful, empirical antibiotics are often started before laboratory confirmation. This practice is clinically understandable, but prolonged treatment in culture-negative cases increases antimicrobial exposure and contributes to antibiotic selection pressure [5,6].

Blood culture remains the reference standard for confirming bacterial sepsis, yet it has important practical limitations. Low blood volume, low bacterial density, prior maternal or neonatal antibiotic exposure and delayed reporting reduce its clinical utility during the early decision window [7]. Therefore, biomarkers that are inexpensive, rapid and locally available remain valuable adjuncts, particularly in resource-limited neonatal units.

C-reactive protein is an acute-phase reactant synthesized by hepatocytes in response to inflammatory cytokines. Its concentration usually rises after the onset of inflammatory stimulation and has been widely used as a supportive test in neonatal sepsis evaluation [8,9]. A single CRP value has limitations, especially early in infection, but an elevated value can strengthen clinical suspicion when correlated with culture results, hematological findings and the clinical condition of the neonate [10,11].

In parallel, pathogen distribution and antimicrobial susceptibility patterns vary across institutions and change over time. Indian and other low-resource neonatal intensive care units often report Gram-negative predominance, particularly *Klebsiella pneumoniae*, *Escherichia coli* and other Enterobacterales, with increasing resistance to first-line and cephalosporin antibiotics [12-14]. Local antibiogram-based policies are therefore essential for empirical therapy and stewardship.

The present study was conducted to evaluate CRP as an adjunct diagnostic biomarker in suspected neonatal sepsis and to

correlate CRP status with blood culture positivity and antibiotic susceptibility patterns among bacterial isolates in a tertiary care teaching hospital.

Materials and methods

Study design and setting

This prospective cross-sectional study was conducted over 12 months from January 2024 to December 2024 in the Neonatal Intensive Care Unit (NICU) of Government General Hospital, Suryapet, Telangana, India. The hospital is a tertiary care teaching hospital attached to Government Medical College, Suryapet, and provides round-the-clock emergency and inpatient services, including paediatric, obstetric, paediatric intensive care, and neonatal intensive care services. Participant recruitment, clinical assessment and blood collection were undertaken in the NICU. CRP estimation, blood culture, isolate identification and antimicrobial susceptibility testing were performed in the Department of Microbiology, Government Medical College, Suryapet.

Study population and sample size

The study population included neonates aged 28 days or less who were admitted to the NICU with clinical suspicion of sepsis. The sample size was determined using a time-bound consecutive census approach rather than a separate formula-based target. All neonates who met the predefined eligibility criteria during the 12-month study period were included, yielding a final sample of 302 neonates. Thus, the sample of 302 represented the complete eligible cohort enrolled during the predefined recruitment period.

Sampling technique

Consecutive sampling was used. Every neonate admitted to the NICU with clinical suspicion of sepsis during the study period was assessed against the predefined eligibility criteria, and each eligible neonate was enrolled through the end of the 12-month recruitment period.

Eligibility criteria

Neonates with clinical features suggestive of sepsis, including fever, hypothermia, lethargy, poor feeding, respiratory distress, apnea or irritability, were included. Neonates with relevant perinatal risk factors such as prematurity, low birth weight, prolonged rupture of membranes, maternal fever or birth asphyxia were also considered eligible. Neonates with major congenital anomalies, those who had received antibiotics before sample collection and those with inadequate clinical or laboratory data were excluded.

Clinical evaluation and sample collection

Demographic details, maternal history, perinatal risk factors and clinical features suggestive of sepsis were recorded using a structured proforma. Approximately 1-2 mL of venous blood was collected aseptically before initiation of antibiotic therapy. Skin disinfection was performed using 70% isopropyl alcohol followed by povidone-iodine. The collected blood sample was used for CRP estimation and blood culture.

CRP estimation

Quantitative CRP estimation was performed using the RHELAX-CRP latex agglutination method. The test is based on antigen-antibody reaction between CRP in serum and latex particles coated with anti-human CRP antibodies. Results were interpreted according to manufacturer instructions. A CRP value greater than 6 mg/L was considered elevated and suggestive of inflammatory response.

Blood culture and isolate identification

Blood samples were inoculated into appropriate culture media and incubated under aerobic conditions. Subcultures were performed on Blood agar and MacConkey agar after 24-48 hours of incubation. Plates were examined for growth, and isolates were identified using colony morphology, Gram staining and standard biochemical reactions, including catalase, coagulase, oxidase, indole, citrate, urease and sugar fermentation tests, as applicable.

Antibiotic susceptibility testing

Antibiotic susceptibility testing was performed by the Kirby-Bauer disc diffusion method on Mueller-Hinton agar. Results were interpreted according to Clinical and Laboratory Standards Institute recommendations [15]. Antibiotics tested included amikacin, gentamicin, cefotaxime, ceftriaxone, piperacillin-tazobactam, imipenem, penicillin, ceftiofur, vancomycin, linezolid and erythromycin, according to organism group.

Quality assurance

All laboratory procedures were performed according to standard operating protocols. Culture media and reagents were quality-checked before use, and standard reference strains were used wherever applicable for quality control of microbiological procedures.

Bias

Potential sources of bias were addressed prospectively. Selection bias was minimized by consecutive enrolment of all eligible neonates throughout the predefined study period. Measurement bias was reduced by use of a structured data-collection proforma, standardized pre-antibiotic blood sampling, a uniform CRP assay method, standard operating procedures for culture and isolate identification, and CLSI-based interpretation of antimicrobial susceptibility testing. All enrolled neonates underwent both CRP testing and blood culture, thereby reducing the risk of partial verification bias. Laboratory quality-control procedures were applied consistently across samples.

Data analysis

Data were entered in Microsoft Excel and analyzed using descriptive statistics. Categorical variables were expressed as frequency and percentage. Diagnostic performance of CRP was assessed by calculating sensitivity, specificity, positive predictive value and negative predictive value using blood culture as the reference standard. Association between CRP status and blood culture positivity was assessed using the chi-square test, and a p-value <0.05 was considered statistically significant.

Ethical considerations

The study protocol was approved by the Institutional Ethics Committee, Government Medical College, Suryapet, Telangana, India, before commencement of the study. Written informed consent was obtained from the parents or legal guardians of participating neonates. Confidentiality of patient-related data was maintained throughout the study.

Results

Participant flow

During the 12-month study period, 302 neonates with clinical suspicion of sepsis were assessed against the predefined eligibility criteria. All 302 were considered potentially eligible and fulfilled the criteria for enrolment; no post-screening exclusions were documented in the available study dataset. Consequently, 302 neonates were enrolled and included in the final CRP-blood culture analysis (Figure 1).

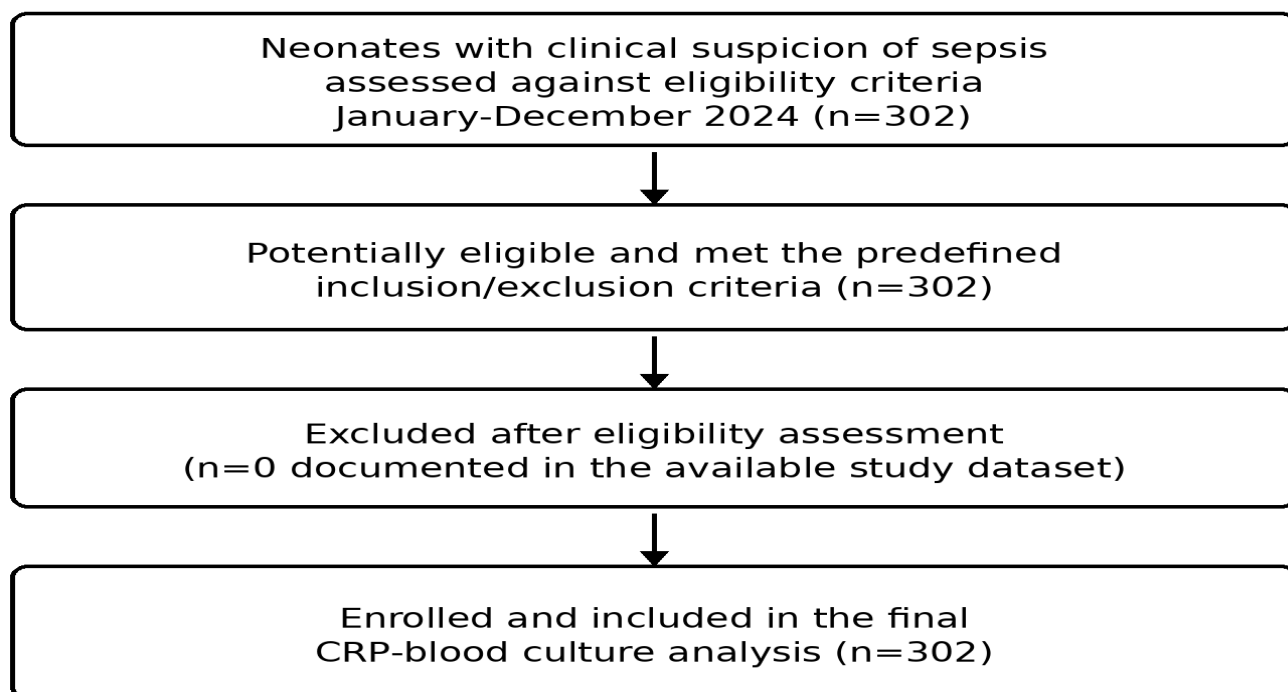


Figure1. Participant flow through eligibility assessment, enrolment and final analysis

Following the participant flow described above, the study population included 178 males (58.9%) and 124 females (41.1%). Low birth weight was present in 186 neonates (61.6%), while 164 neonates (54.3%) were preterm. Among culture-

positive neonates, early-onset sepsis accounted for 42 cases (60.0%) and late-onset sepsis for 28 cases (40.0%), as shown in Table 1.

Table 1: Demographic and clinical profile of neonates

Variable	Category	Number (n)	Percentage (%)
Sex	Male	178	58.9
	Female	124	41.1
Birth weight	<2.5 kg (low birth weight)	186	61.6
	>=2.5 kg	116	38.4
Gestational age	Preterm (<37 weeks)	164	54.3
	Term (>=37 weeks)	138	45.7
Sepsis onset pattern among culture-positive cases	Early-onset sepsis	42	60.0
	Late-onset sepsis	28	40.0

Note. Percentages for sepsis onset pattern are calculated among the 70 culture-positive neonates.

Blood culture was positive in 70 of 302 neonates, giving a culture positivity rate of 23.2%. Gram-negative bacteria were isolated in 48 cases (68.6%), while Gram-positive bacteria were isolated in 22 cases (31.4%). *Klebsiella pneumoniae* was the most frequent

organism, followed by *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and coagulase-negative staphylococci, as summarized in Table 2.

Table 2: Blood culture positivity and bacteriological profile

Parameter	Category/Organism	Number (n)	Percentage (%)
Blood culture result	Culture positive	70	23.2
	Culture negative	232	76.8
Organism group among positive cultures	Gram-negative bacteria	48	68.6
	Gram-positive bacteria	22	31.4
Isolated organism	<i>Klebsiella pneumoniae</i>	24	34.3
	<i>Escherichia coli</i>	14	20.0
	<i>Pseudomonas aeruginosa</i>	10	14.3
	<i>Staphylococcus aureus</i>	12	17.1
	Coagulase-negative staphylococci	10	14.3

Antibiotic susceptibility testing among Gram-negative isolates showed highest sensitivity to imipenem (91.7%) and piperacillin-tazobactam (79.2%). Amikacin sensitivity was 75.0%.

Resistance was high against ceftriaxone (66.7%) and cefotaxime (64.6%), indicating reduced activity of third-generation cephalosporins in the present isolate profile (Table 3).

Table 3: Antibiotic susceptibility pattern among Gram-negative isolates (n = 48)

Antibiotic	Sensitive (%)	Resistant (%)
Amikacin	75.0	25.0
Gentamicin	62.5	37.5
Cefotaxime	35.4	64.6
Ceftriaxone	33.3	66.7
Piperacillin-tazobactam	79.2	20.8
Imipenem	91.7	8.3

Among Gram-positive isolates, vancomycin and linezolid showed complete sensitivity. Cefoxitin sensitivity was 68.2%, whereas penicillin resistance was high at 72.7%. Erythromycin

showed moderate activity, with 54.5% sensitivity and 45.5% resistance (Table 4).

Table 4: Antibiotic susceptibility pattern among Gram-positive isolates (n = 22)

Antibiotic	Sensitive (%)	Resistant (%)
Penicillin	27.3	72.7
Cefoxitin	68.2	31.8
Vancomycin	100.0	0.0
Linezolid	100.0	0.0
Erythromycin	54.5	45.5

CRP was elevated in 50 of 70 culture-positive neonates (71.4%). Among culture-negative neonates, 18 had elevated CRP and 214 had normal CRP. Using blood culture as the reference standard, CRP had a sensitivity of 71.4%, specificity of 92.2%, positive

predictive value of 73.5% and negative predictive value of 91.5%. The association between elevated CRP and blood culture positivity was statistically significant ($p < 0.001$), as shown in Table 5.

Table 5: CRP-blood culture correlation and diagnostic performance

CRP status	Culture positive	Culture negative	Total
Elevated CRP (>6 mg/L)	50	18	68
Normal CRP	20	214	234
Total	70	232	302

Table 6: (continued) Diagnostic indices of CRP

Parameter	Value (%)
Sensitivity	71.4
Specificity	92.2
Positive predictive value	73.5
Negative predictive value	91.5

Chi-square test for CRP status versus blood culture result: $p < 0.001$.

Discussion

The present study evaluated CRP as an adjunct diagnostic marker in 302 neonates with suspected sepsis and correlated CRP status with culture results and antibiotic susceptibility patterns. Blood culture positivity was 23.2%, which reflects a clinically relevant

burden of microbiologically confirmed sepsis among symptomatic neonates. Culture positivity in neonatal sepsis varies widely across studies because of differences in case definition, blood volume, prior antibiotic exposure, population risk profile and laboratory methods [2,3,7].

The predominance of Gram-negative bacteria in the present study is consistent with reports from Indian and other low- and middle-income neonatal units. *Klebsiella pneumoniae* was the leading isolate, followed by *Escherichia coli* and *Pseudomonas*

aeruginosa. This distribution is important because Gram-negative neonatal sepsis is frequently associated with severe disease, limited therapeutic options and higher antimicrobial resistance burden [12-14,16].

The susceptibility pattern showed high resistance to cefotaxime and ceftriaxone among Gram-negative isolates, while imipenem and piperacillin-tazobactam retained better activity. This pattern supports the need for institution-specific antibiograms rather than continued reliance on fixed empirical regimens. However, preserved carbapenem sensitivity should not encourage unrestricted use; carbapenems must be protected through stewardship policies, escalation criteria and culture-guided de-escalation [14,17].

In Gram-positive isolates, vancomycin and linezolid showed complete sensitivity, while penicillin resistance was high. The cefoxitin result indicates that methicillin resistance screening remains relevant among staphylococcal isolates. These findings reinforce the value of organism-wise susceptibility testing in neonatal units, where empirical coverage must be balanced against the risk of selecting resistant pathogens.

CRP showed 71.4% sensitivity and 92.2% specificity in this study. The high specificity indicates that elevated CRP, when interpreted with clinical features, can support the diagnosis of bacterial sepsis. The high negative predictive value is also clinically useful because normal CRP in a stable neonate can assist antibiotic review when culture is negative and clinical suspicion falls. However, a single CRP result should not be used in isolation because CRP rises after an inflammatory lag period and can be influenced by non-infectious perinatal factors [8-11,18].

The statistically significant association between elevated CRP and culture positivity supports its role as a practical adjunct to blood culture. In settings where advanced molecular diagnostics or rapid biomarker panels are not routinely available, CRP remains accessible, inexpensive and easy to interpret. Its greatest value lies in an integrated sepsis evaluation pathway that combines clinical assessment, blood culture, CRP trend, hematological parameters and local microbiology data [6,8,19].

The present findings also have stewardship implications. Antibiotics are frequently continued in neonates because of diagnostic uncertainty. A structured protocol using CRP trends with culture results can help clinicians reassess antibiotic need, reduce unnecessary exposure in culture-negative neonates and support timely targeting of therapy in culture-positive cases [6,17,20].

Generalizability

The findings are most applicable to tertiary care neonatal intensive care units with comparable patient profiles, culture-based microbiology facilities and latex agglutination-based CRP testing. The bacteriological spectrum and antibiotic susceptibility pattern should be interpreted locally because pathogen distribution and antimicrobial resistance vary across hospitals, referral patterns, infection control practices and antibiotic policies.

Conclusion

This prospective cross-sectional study showed that CRP is a useful adjunctive biomarker in suspected neonatal sepsis. Culture positivity was 23.2%, with Gram-negative bacteria forming the dominant isolate group and *Klebsiella pneumoniae* being the most common pathogen. CRP demonstrated high specificity, acceptable sensitivity and a significant association with blood culture positivity. The observed resistance to third-generation cephalosporins highlights the importance of continuous antibiogram surveillance. Combining CRP with blood culture and local susceptibility data can strengthen early diagnosis, guide empirical therapy and support antimicrobial stewardship in NICU practice.

Limitations

This was a single-center study with 302 neonates and culture-based microbiological confirmation. Serial CRP trends, procalcitonin, interleukin markers and molecular diagnostic methods were not assessed. Blood culture yield depends on sample volume and timing of collection. Maternal antibiotic exposure, clinical severity scores and treatment outcomes were not analyzed in detail. Long-term neonatal outcomes were outside the study scope.

Recommendations

CRP should be included as a supportive test in neonatal sepsis screening protocols, especially where rapid molecular tests are unavailable. CRP results should be interpreted with clinical features, blood culture and hematological findings rather than as a stand-alone diagnostic test. Every NICU should maintain a periodically updated local antibiogram to guide empirical antibiotic choices. High resistance to third-generation cephalosporins should prompt regular review of empirical therapy policies. Carbapenems and other broad-spectrum antibiotics should be reserved for clear indications and reviewed after culture results. Serial CRP monitoring can be incorporated into antibiotic review protocols for clinically stable culture-negative neonates. Larger multicentric studies should evaluate

CRP in combination with other biomarkers and include neonatal outcomes.

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Abbreviations

AST: Antibiotic susceptibility testing;

CLSI: Clinical and Laboratory Standards Institute;

CONS: Coagulase-negative staphylococci;

CRP: C-reactive protein;

NICU: Neonatal Intensive Care Unit;

Source of funding

The study had no funding.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Dr Sri Dharani Munagala contributed to study conception, clinical data collection, sample coordination, microbiological processing, data recording, literature review and drafting of the manuscript.

Dr Aditi Tomer Thakur contributed to study design, supervision of laboratory methods, data interpretation, manuscript preparation and critical revision of intellectual content.

Dr S Ruth Ramya contributed to microbiological methodology, quality assurance, data analysis, literature review and revision of the manuscript.

Dr Taruni provided overall academic supervision, guidance in study planning, interpretation of findings and final critical review of the manuscript.

Dr R Kondal Rao contributed to supervision, data interpretation, formal analysis and critical revision

Dr Nagasaikaran Sade provided literature review, data analysis and drafting of the manuscript.

Data availability

Data available on request

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