

# Evaluation of C-reactive protein for identification of neonatal sepsis in co-relation with blood culture

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## Abstract

**Background:** CRP can be used as early marker for diagnosis of neonatal sepsis guiding in early intervention and management and preventing neonatal mortality and morbidity. **Methods:** In this observational prospective study a total of 300 neonates with diagnosed sepsis were included. Out of this 204(68%) had positive CRP and 156(52%) had positive blood culture. **Results:** CRP was positive in 68% neonate and negative in 32% neonate with the sensitivity 85.26% and specificity was 50.69%. The PPV was 65.20% and NPV was 76.04%. Blood culture was negative in 48% neonates. Klebsiella (25.66%) was the most common organism positive on blood culture followed by MSSA (11.66%), MRSA (3.66%) and E Coli (3.66%). **Conclusion:** CRP have high sensitivity and has high predictive value as compared to blood culture in diagnosing neonatal sepsis and hence can be used in routine clinical practice to diagnose neonatal sepsis early and to start with antibiotic to prevent morbidity or associated mortality.

**Keywords:** C-Reactive Protein, Acute Phase Reactant, Infection, Neonatal Sepsis.

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sepsis and approximately 1% die of sepsis related causes<sup>2</sup>. Sepsis related mortality is largely preventable with rational antimicrobial therapy with aggressive supportive care.

## METHODS

In this observational prospective study 300 neonates who were suspected of neonatal sepsis were included and studied

### Selection criteria

Participants were selected based from the following selection criteria

### Inclusion criteria

Neonates with 3 or more than 3 of following signs or symptoms, septicaemia is suspected and will be include in study. Refusal of feeds, Abdominal distention, Vomiting, Lethargy, Jaundice, Poor cry, Seizures, Diarrhea, Apnea, Tachypnea, Poor capillary refill, Hypothermia, Fever, Umbilical discharge, Not arousable, comatosed, Sclerema, Poor weight gain, Shock, Bleeding, Renal failure, Cyanosis, Chest retractions, Grunts, Blank look, Excessive crying/irritability

## INTRODUCTION

Neonatal sepsis is a clinical syndrome of bacteraemia characterized by systemic signs and symptoms of infection in the first month of life.<sup>1</sup> Neonatal sepsis encompasses systemic infections of the newborn including septicaemia, meningitis and pneumonia. It is the commonest cause of neonatal mortality and is probably responsible for 30-50% of the total neonatal deaths each year in developing countries<sup>2</sup>. It is estimated that 20% of all neonates develop

### Bulging fontanelle

1. Parents of neonates who are ready to give informed consent
2. Parents of neonates who are willing to participate in the study

### Exclusion criteria

1. Neonates who had undergone any surgical operation.
2. Neonates who had exchange transfusion.
3. Neonates who had received parenteral antibiotics therapy before admission
4. Neonate of mothers who had intrapartum antibiotics within 1 week of delivery
5. Parents of neonates who are not willing to participate in the study

### Sample size

300 neonates with diagnosed case of sepsis.

- Calculated for 97% sensitivity and 95% specificity for CRP test against the gold standard test i.e. blood culture. The sample size was calculated by using formula
- $(a+c)=Z^2S(1-S)/d^2$
- (source- Patrikar S-in Textbook of Public Health Community Medicine 1<sup>st</sup> edition 2009 Ed bhalwarR. dept of community medicine, AFMC, Pune WHO India Office, New Delhi)
- $(a+b+c+d)=P(a+c)$  for both sensitivity and specificity
- Where S=estimated sensitivity/specificity, d=absolute precision, P=prevalence of disease, a+c=minimum total disease positive cases, b+d=minimum total disease negative cases, Z= z value associated with alpha
- Higher among those was sensitivity sample (299) as compared to specificity sample<sup>3</sup>
- So, the sample size for this study is 299, which was approximated to 300.

### METHODOLOGY

The study was initiated after obtaining approval from the institutional ethics committee and department of paediatrics. After obtaining valid written consent from parent's clinical findings were documented and thorough clinical examination was done. The findings were recorded on proforma, specially designed for the study. Sepsis was suspected as per the symptoms and signs included in inclusion criteria. CRP and blood culture were examined at the time of admission before starting of antibiotics. C-reactive protein was estimated qualitatively using the CRP latex kit. The specific performance characteristics of the CRP latex reagent was standardized to detect serum CRP levels at or above 6mg/l, which is considered the lowest

concentration of clinical significance. Half a milliliter of venous blood was collected in plain bottles and centrifuged. C-reactive protein was estimated using a drop of undiluted serum placed onto the circle of the agglutination slide with the use of disposable pipettes provided in the kit. The results were read using the positive and negative controls as reference for agglutination. Visible agglutination of latex particles constituted a positive result which indicated a level of CRP equal or more than 6 mg/l while negative result was reverse. Blood culture was done for all neonates using two milliliters of venous blood collected from peripheral vein after adequate skin preparation and before the commencement of antibiotics. The blood was aseptically introduced into culture media. The specimen was processed according to standard methods in the microbiology laboratory<sup>3</sup>. Inoculated blood culture media was considered negative if there was no growth after continuous incubation for up to 5 days, subcultures being made each day. Antibiotic sensitivity was done using Kirby-Bauer disc diffusion method. The results of laboratory investigations and other relevant data such as age, sex, birth weight and gestational age as well as symptoms present and risk factors for sepsis of recruited babies was recorded in a proforma. The results were analyzed. The sensitivity, specificity, positive and negative predictive values of CRP was calculated.

### Statistical analysis

Data was recorded in a predesigned proforma and compiled in Microsoft excel version 2015 and analyzed. Descriptive statistics for quantitative variables was represented as mean +/- SD. Graphical representations were done wherever applicable. Level of significance was considered as P≤0.05. Software used for analysis was Graph pad prism.

**Ethical approval:** The study was approved by the institutional ethics committee

### RESULTS

During study period, total 300 neonates admitted in neonatal intensive care unit were studied. Out of this 204(68%) had positive CRP and 156(52%) had positive blood culture. Klebsiella (25.66%) was the most common organism positive on blood culture followed by MSSA (11.66%), MRSA (3.66%) and E Coli (3.66%). According to table no 1, blood culture is considered to be the gold standard in diagnosing sepsis so we compared CRP and blood culture also we found that the sensitivity of CRP was 85.26% and specificity was 50.69%, PPV was 65.20% and NPV was 76.04 %. As per table no 2 the average age of neonate in this study was  $3.49 \pm 3.72$  days with majority (68.33%) of the neonates being ≤ 3 days old. Thus, the incidence of sepsis in early neonatal period was high in this study. This can be compared to study conducted by

Zakariya BP *et al.*<sup>6</sup> where the average age of enrolled neonates were  $5.85 \pm 7.15$  days with majority 69 cases (57.5%) were early-onset and 51 cases (42.5%) were late-onset sepsis. Mersha A *et al.*<sup>7</sup> in their study reported 66.7% incidence of early onset sepsis whereas Varsha *et al.* in their study [5] reported 47.6% incidence of early neonatal sepsis. Male neonates were in majority (69.33%) in this study, with the male to female ratio as 2.26:1. The above findings consistent with the study conducted by Pradeep Verma *et al.*<sup>8</sup> where 65.27% neonates were male and 34.72% were females, with the male: female ratio was 1.87:1. Similar male preponderance was reported by Woldu MA *et al.*<sup>9</sup> and Zakariya BP *et al.*<sup>6</sup>, where 55.2% and 58.3% neonate respectively were male. The factors regulating the synthesis of gamma globulin are probably situated on X chromosomes in the male infants thus confers less immunological protection compare to female counterpart.<sup>10</sup> Blood culture was negative in 48% neonate in this study, among those with positive blood culture

according to table no 3 Klebsiella was the most common organism grown (25.66%) followed by MSSA (11.66%), MRSA (3.66%) and E Coli (3.66%). Similar report was highlighted in study conducted by Pradeep Verma *et al.* [8] where Klebsiella was the most common organism reported followed by Strep faecalis and Coagulase negative Staphylococci. The blood culture was positive in 45.2% of septicemic neonates. Similar to our study Klebsiella was found most common organism in study done by Desai *et al.*<sup>10</sup> (47.14%), Rathore *et al.*<sup>11</sup>(55.14%). The etiological agents of neonatal sepsis vary between developed and developing countries. Klebsiella pneumoniae and other Gram-negative organisms were the common causes of sepsis in the present study as well other studies from India and Nigeria<sup>12,13</sup>. However, in the developed countries Group B Streptococcus and coagulase negative staphylococci (CONS) are the predominant causes of sepsis.<sup>14</sup>

**Table 1:** Assessing predictive value of CRP

CRP	Culture positive	Culture negative
Positive	133	71
Negative	23	73
Sensitivity		85.26%
Specificity		50.69%
Positive predictive value		65.20%
Negative predictive value		76.04%

**Table 2:** Age and gender wise distribution

AGE(DAYS)	MALE	FEMALE	NO OF PATIENTS	PERCENTAGE
≤3 days	142	63	205	68.33
4-7	46	20	66	22
8-14	15	8	23	7.66
>=15	5	1	6	2
Total	206	92	300	100
average age			3.49±3.72	
Median age (range)			2 (1to 23)	

**Table 3:** Blood culture among enrolled patients

CULTURE	NO OF PATIENTS	PERCENTAGE
Negative	144	48
Klebsiella	77	25.66
MSSA	35	11.66
MRSA	11	3.66
CNSA	6	2
E.coli	11	3.66
Pseudomonas	4	1.33

## DISCUSSION

Sepsis is one of the commonest cause of mortality and morbidity among the neonate in NICU. It ranks among the three commonest illnesses affecting babies and ranks as the top most illness for neonatal mortality especially amongst low birth weight and premature babies.<sup>5</sup> Neonatal sepsis

may be difficult to differentiate from other conditions, because the clinical signs are non-specific. Neonatal sepsis with its high mortality and morbidity despite the use of higher antibiotics and advanced supportive care still remains a diagnostic and treatment challenge to the health care providers. An early and prompt diagnosis helps in the

institution of therapy at the earliest and also prevents the unnecessary use of antibiotics thereby keeping the emergence of drug resistance in check. Delay of even few hours in initiating treatment can increase morbidity and mortality considerably.<sup>5</sup> Conventional methods do not provide a rapid diagnosis. So, there is a need for rapid diagnostic test to initiate early antibiotic therapy and prevent morbidity and mortality. Sepsis screen tests involving CRP form a simple, cheap, rapid and easily available parameters with reasonable diagnostic accuracy. On this basis early and rational antibiotics therapy can be started in critical septicemic infants. Hence the present study was conducted to evaluate the correlation of CRP with blood culture in neonate with sepsis.

## CONCLUSION

The sensitivity of CRP was 85.26% and specificity was 50.69%. The Positive predictive value was 65.20% and Negative predictive value was 76.04 % CRP shows strong positive correlation with blood culture and was highly significant p value (0.0001).

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